Migraine and Biogenic Amines
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Abstract

Objective: Migraine emerges as one of the major causes of headache in today’s world. It is a disease that is often characterized by a moderate or severe one-sided headache, nausea, or vomiting as well as sensitivity to light, and sound. According to the World Health Organization (WHO), it is among the first 20 diseases that reduce individuals’ working capacity. Various factors may affect the formation of migraines, such as hormonal changes, stress, hunger, fatigue, sleeping disorders, and weather conditions. The mechanisms by which these factors trigger migraine in a patient have been popular research topics recently. Materials & Methods: It is generally acknowledged that the central nervous system is greatly affected by these factors. The possible potential mechanisms of migraine impact on human health, MEDLINE, Embase, the Cochrane Central, www.ClinicalTrials.gov, PubMed, Science Direct, Google Scholar, and selected websites including) and databases were examined. Results: Various theories have been proposed regarding the formation of migraine. Among these major theories are vascular theory, neurological theory, neurovascular theory, and biochemical theory. Scientific research usually focuses on these four leading theories. Although some migraine patients may suffer from headache attacks that occur without a reason, most migraine attacks are usually caused by internal or external factors. It was reported that while a single triggering factor might cause migraine attacks in some patients, others might suffer from migraine attacks occurring because of several triggering factors. The relationship between migraine and nutrition is a complex issue. Some substances in nutritional elements may affect nerve tracts and thus cause headaches by creating a vasoconstrictor or vasodilator effect. Various chemicals in different nutritional elements were held responsible for migraine attacks. Because tyramine, phenylethylamine, and histamine are considered to play a role in headache triggering mechanisms, biogenic amines, and nutritional elements such as cheese, chocolate, and red wine containing these chemicals can be considered as important triggering factors too. Conclusions: The present study analyzes the impact of biogenic amines such as histamine, tyramine, and phenylethylamine on migraine attacks.

Keywords: Migraine and Biogenic Amines

Introduction

Migraine is one of the most common reasons for headaches nowadays. [1] Derived from the Greek word ‘hemicrania’, the words have been used in its French pronunciation ‘migraine’ since the 18th century. [2] The disease is generally characterized by a moderate or severe one-sided headache, nausea or vomiting, sensitivity to light, and sound. [3] While migraine prevalence in men is 6 to 9%, the same percentage is 15% to 25% for women around the globe.[4] According to WHO data, 18% of women in the world suffer from migraine attacks. [5] It has been also reported that migraine is twice as prevalent in women as men and thus women experience more severe migraine headaches compared to men. [6] WHO data also indicate that migraine is the 19th disease that reduces individuals’ working capacity around the world, and it is ranked in the 12th place for women. [7] The reason for the difference between sexes in terms of migraine prevalence has not been exactly revealed yet. It is argued that women suffer from migraines more than men due to their hormonal differences. [8] The International Headache Society (IHS), which publishes international criteria for the classification of migraines, listed several standard criteria for migraine diagnosis and treatment in ICHD-II. [9] In this document, migraine was divided into six major categories. The first migraine subtype among the most common migraine types in the world is ‘simple migraine’ or ‘migraine without aura’, while the second subtype is ‘typical migraine’ or ‘migraine with aura’. [10] Aura can be defined as a mix of neurological symptoms occurring in certain parts of the head before during or, rarely, following a migraine attack. [9] Its symptoms usually develop within five minutes, and last less than 60 minutes. While patients may sometimes suffer from headache for 60 minutes following the occurrence of aura, it may also be delayed for a few hours or may not occur at all. [11,12] In addition migraines can be divided into two categories, that is episodic, and chronic, depending on headache frequency. While, in episodic migraine, patients suffer from headaches for less than an average of 15 days each month in the last three months,

chronic migraine occurs for more than an average of 15 days or at least for eight days each month in the last three months. Various factors may affect the formation of migraines. The leading factors are hormonal changes, stress, hunger, fatigue, sleeping disorders and weather conditions. The impact of these factors on migraine triggering mechanisms has been a popular research topic in recent years. It is generally argued that these factors create an effect on patients’ central nervous systems. One of the foremost theories about the formation of migraine as a disease is vascular theory, which still maintains its validity today. According to vascular theory, migraine is experienced because of electrochemical disorder, which occurs due to intracranial vasoconstriction followed by vasodilation. As a result of these electrochemical disorders, various substances secreted by nerves cause inflammation. The second most popular theory is neurological theory, argues that migraine attacks occur due to the overstimulation of different neurons, which is caused by various changes in the neurotransmission system. Neurovascular theory is the third most popular theory and argues that migraine is caused by the release of inflammatory neuropeptides from the trigeminal system, which indicates neurovascular events. Besides, it has also been argued that due to changes in the hypophysis, its pressure on the trigeminal nerve may also lead to migraine attacks. Another popular theory is the biochemical theory, which argues that migraine attacks occur because of decreasing blood serotonin levels. In parallel with this theory, thrombocyctic theory was also proposed, as serotonin is stored in thrombocytes. According to thrombocyctic theory, migraine attacks are caused by thrombocyte dysfunction.

### Materials and Methods

A literature search was carried out through MEDLINE, Embase, the Cochrane Central, www.ClinicalTrials.gov, PubMed, Science Direct, Google Scholar, and selected websites including) and the World Health Organization (WHO).

Migraine commonly effects all over the world were included in the study. The reference articles were obtained from databases using key words such as “migraine attack, biogenic amines, nutrient” to collect existing information. The sub-references of the selected articles via the keywords were researched and these articles were examined as well. In studies on a migraine, primarily clinical human studies, laterally animal studies have been analyzed. The research, meta-analyses, and reviews have been the basis for the current work.

### Triggering factors

Headache attacks may emerge without a particular reason in some migraine patients with migraine. However, most migraine attacks are often caused by internal factors such as hormonal changes or external factors such as weather conditions and some odors. Triggering factors do not affect all patients at a similar level. While a single triggering factor may lead to headaches in some patients, a mix of various factors may cause headaches in other patients. It was reported that these triggering factors were effective by 90% in migraine without aura and by 60% in migraine with aura. Migraine may also be caused by dietary factors such as stress, menstruation, hormonal changes and skipping meals, sleep patterns (insomnia or hypersomnia), environmental factors, fatigue, weather conditions (humidity, pressure, wind, etc.), alcohol (particularly beer and wine), various odors (perfumes or other strong chemicals), brightness, smoke, high altitude, coughing, and some other nutritional elements. It was reported in various studies that a single triggering factor might lead to migraine attacks in some patients, while a mix of various factors might be responsible for these attacks in other patients. Additionally, it is also known that sodium nitrite, which is used in instant foods for food coloring, botulism prevention, may cause headaches in some individuals, which may be related to nitric oxide release and resulting validation. In this respect, individuals who are sensitive to these foods are recommended to keep away from nutritional elements containing sodium nitrite, sodium nitrate, potassium nitrate, or potassium. There is a complex relationship between migraine and nutrition. Foods may affect nerve tracts and thus cause headaches by creating a vasoconstrictor or vasodilator effect due to some substances that they contain. In daily nutrition, although skipping meals and hunger are considered as critical triggering factors, other nutritional elements such as caffeine, dairy products, alcoholic beverages (alcohol consumption is a particular triggering factor in younger individuals), fermented products, chocolate, foods containing tyramine, and nitrite, citrus fruits, monosodium glutamate, aspartame, food coloring, and additives usually causing of migraine attacks. Additionally, some chemicals in various foods also lead to migraine attacks. For instance, because tyramine, phenylethylamine and histamine are considered to play a certain role in headache triggering mechanisms, biogenic amines and foods containing these chemicals such as cheese, chocolate and red wine are also widely accepted among important triggering factors.

### Biogenic amines

Biogenic amine is organic based, biologically active, and nitrogenous compounds with low molecular weights. They are formed by decarboxylation of amino acids or animation and transamination of ketones and aldehydes, all of which emerge because of metabolic activities in plants, animals, and microorganisms. They are called biogenic amines because they are formed by the metabolic activities of living organisms. An amine of an amino acid emerges because of metabolic activities in animals and humans. However, excessive intake of...
biogenic amines may cause human body to overrun its natural amine detoxification capacity and thus it tends to result in some toxic effects in the body. Protein-rich foods and fermented products are included in risk groups in terms of the formation of biogenic amines. Protein-rich foods such as meat and fish products, egg, cheese, soy products, fermented vegetables, alcoholic beverages, citrus fruits, nuts, and chocolate can be given as major examples of nutritional elements containing biogenic amines. Some foods containing biogenic amines such as histamine, tyramine, phenylethylamine, putrescine, cadaverine, spermine play an important role in human metabolism. Among these biogenic amines, histamine, tyramine and phenylethylamine are particularly correlated with migraine and headache attacks.

**Histamine and migraines**

Discovered by Dale and Laidlaw in 1910, histamine is an amine emerging because of histidine decarboxylation. It is metabolized by N-methyl transferase enzyme and synthesized and stored in mast cells and basophils. It is also the amine with the highest number of biological activities. It stimulates gastric secretion, smooth muscle contraction, vasodilation, permeability, and many other processes and plays a certain role in both immunological and physiological multiple mechanisms. Histamine displays its effects on biological activities through the cardio-vascular system and connecting cell membrane receptors in various secretory glands.

The relationship between histamine and headaches has been studied for more than a few centuries. Numerous studies have been so far carried out to analyze the headache induction activity of histamine and the impact of antihistamines on the treatment of headaches. The theory about the relationship between migraine and histamine is accredited to Horton. This theory argues that histamine levels increase during a headache attack, resulting in a higher histamine level in the post-headache period. It can be thus stated that migraine is related to the degranulation of mast cells.

When the link between headaches and histamine in migraine patients is analyzed, it can be observed that brain vessels are exposed to vasodilation because of histamine, which eventually results in a headache attack. Wantke et al. applied a diet that does not contain any histamines to 28 migraine patients for 4 weeks and found that headache attacks in 19 patients were reduced by 50% or more following the diet. In addition, the number of headache attacks and analgesic drug intake declined significantly due to the diet. Histamine has been analyzed in detail along with cytokines, chemokines and vasoactive peptides to gain insight into the underlying cellular mechanisms that cause migraine attacks and help them persist. The correlation between migraine, which forms mast cell degranulation and neurogenic inflammation is widely accepted. Under normal circumstances, histamine can be easily digested owing to amine oxidase and conjugation activities. Following the digestive process, the detoxification system functions to metabolize histamine formed by intestinal bacteria. This process is carried out by some enzymes such as diamine oxidase, monoamine oxidase and N-methyl transferase, which transform histamine into non-toxic substances. This mechanism is sufficient for a normal diet. However, the system is disturbed by a high level of histamine consumption or the use of monoamine oxidase inhibitors, resulting in various toxic effects.

Histamine is one of the major toxic amines found in protein-rich foods such as cheese, meat and fish products. It can also be found in various fish products such as anchovy, mackerel, and tuna fish (dark meat fish) and/or oily fish. In addition it is also reported that histamine levels are high in fermented products compared to other types of products. For instance, it may reach 40 mg/liter in cabbage pickle juice. The consumption of foods with a high histamine level may lead to the emergence of some symptoms. Maximum histamine level in nutritional elements is specified as 10-100 mg/100g, whereas the same level for wines is 2-10 mg/L. Maximum histamine level in wines is defined as follows in the following countries: Germany (2 mg/L), Belgium (2 mg/L), France (3.5 mg/L), Australia (10 mg/L) and Switzerland (10 mg).

**Tyramine and migraine**

Tyramine is formed by bacterial activities of tyrosine amino acid and is also called tyramine monoamine due to its chemical properties. Tyramine, which is also known as trace amine in the central nervous system, causes hypertension and diet-induced migraine. In the human body, biogenic amines are transformed into less active substances through decomposition in a detoxification system. Histamine-N-methyl transferase enzymes called Diamine Oxidase (DAO) and Monoamine Oxidase (MAO) function in this system. Tyramine decomposition is performed by some catalytic reactions, as it is often metabolized in the gastrointestinal mucosa and liver. It is found in lower concentrations in the human body compared to histamine. The foremost effects of tyramine are norepinephrine release in sympathetic nervous cells and agonist effects on adrenergic receptors, which trigger headaches. Because enzyme activities are prevented in patients treated with MAO inhibitor drugs, the toxic effects of tyramine are remarkably high. The most common symptoms of tyramine toxicity are tachycardia, hypertensive crisis, hypertension, headaches, and migraine. Also, heart and respiratory failure, edema in the lungs, neural disorders and intracranial hemorrhages are other symptoms that are likely to result in death. Tyramine is one of the most common types of biogenic amines in fermented meat products and is found in cheese types such as cheddar and parmesan, ice cream, smoked products, tuna fish stored at different ambient temperatures, soy sauce, broad bean, yeast, tomato, onion, circus fruits, canned food, fig, coffee, cabbage pickle, excessively ripe fruits as well as some types of beer and wine. The link between tyramine and headaches was first discovered when patients treated with MOA inhibitor drugs suffered from headaches and hypertensive crisis after they consumed cheese with a high tyramine content. Similarly, another study found a correlation between the consumption of food with high tyramine content and acute migraine and severe headaches. When foods that trigger migraine attacks were analyzed, it was found that patients reported migraine or headache attacks by 0% to 19% following cheese consumption.
content in cheese. [71] Although a usual meal contains 40 mg tyramine, under normal physiological conditions, nearly 400 mg tyramine can be consumed by an individual without any visible hypertensive reactions. 8 mg of tyramine may increase blood pressure levels when MAO inhibitors are irreversibly destroyed. [72] When tyramine is consumed without any other nutritional elements, 10 to 80 mg of tyramine may cause swellings on the human body, while amounts higher than 100 mg may result in headaches and migraines. [58,71] EFSA set the standards for tyramine consumption, which does not cause any negative health effects on the human body per meal per person. According to these standards, healthy individuals who do not use MAO inhibitor drugs can consume up to 600 mg per meal. On the other hand, patients using third generation and conventional MAO inhibitor drugs can consume 50 mg and 6 mg tyramine, respectively. [71] In general, tyramine toxicity levels for alcoholic beverages are reported as 25 to 40 mg/L. [76]

**Phenylethylamine and migraine**

While phenylethylamine and other vasoactive amines affect vascular systems directly or indirectly, psychoactive amines such as histamine, putrescine, and cadaverine affect neurotransmitters in the central nervous system. [71] The chemical structure of phenylethylamine indicates that it is an aromatic biogenic amine, theobromine, caffeine, methylxanthines, and catechin phenolic compound. Similar to tyramine, these chemicals affect the norepinephrine release in sympathetic nervous cells and brain blood flow, which eventually causes headache. [64] Biogenic amines do not pose a threat to human health unless consumed in high concentrations. Nevertheless, it may lead to some disorders in genetically flawed individuals with a limited catabolism mechanism. [32] Phenylethylamine can inhibit both diamine oxidase and histamine methyltransferase, demonstrating that the tyrosine decarboxylase enzyme, which affects tyramine, displays a low decarboxylase activity on phenylalanine, too. It is stated that even a low amount of phenylethylamine may cause headaches in patients who do not take any drugs for treatment. [78]

Phenylethylamine reduces monoamine oxidase B activity in migraine patients and causes the release of vasoactive amines such as serotonin and catecholamine. When the amount of these amines increases in the body in parallel with a monoamine oxidase B deficiency, it may lead to migraine attacks. [71] It is reported that an average amount of 30 mg/kg phenylethylamine may result in headaches. [79,80]

Among many food products, cacao and chocolate abound in phenylethylamine. The amounts of phenylethylamine in chocolate made from lightly, moderately, and finely roasted cacao is reported as less than 2.9 mg/100 g, 10 mg/100 g and 12 mg/100 g, respectively. [81] A high amount of phenylethylamine may lead to various symptoms such as headaches, increased blood pressure and skin redness. [43,82,83] Although chocolate is considered as a triggering factor for migraine patients, the role of phenylethylamine has not been fully understood yet. It was argued that caffeine in chocolate products was likely to trigger migraine attacks. [28] However, a study on female patients suffering from chronic headaches reported that chocolate was not a triggering factor for migraine or other types of headache. [44] On the other hand, another study indicated that chocolate was a triggering factor in 20% of the patients suffering from headaches. [43] A theory argues that chocolate, which is considered to trigger migraine attacks, is one of the most easily accessible desserts to please patients’ appetite during the prodromal period of a migraine attack. Therefore, chocolate is assumed to be a triggering factor in attacks due to its coincidence with the occurrence of migraine attacks. [85] [Another assumption is that chemical triggering factors such as caffeine and phenylethylamine in chocolate cause norepinephrine release and change cerebral blood flow, thus leading to headache attacks in patients. [11,33]]

**Serotonin and migraine**

Tryptophan, which is an essential aromatic amino acid, is decarboxylated to 5-hydroxytryptophan by tryptophan hydroxylase enzyme to transform it into 5-hydroxytryptamine or serotonin. [86-89] Serotonin is an aromatic and heterocyclic amine. [90] It is synthesized in the central nervous system and intestines and, as a neurotransmitter, plays a vital role in the regulation of many different physiological functions such as sleeping, thirst, hunger, mood and sexual intercourse. [89,91]

Serotonin can be found in various food products such as strawberries, grape, tomato, orange, pineapple, banana, avocado, olive oil and walnut. [92-94] Noradrenalin, octopamine, dopamine, histamine, serotonin and phenylethylamine are found in banana and banana products. Biogenic amines such as serotonin, histamine and phenylethylamine function as preservative substances (for pest control and mold prevention) in bananas. [88] Serotonin is the most common biogenic amine in unripe fruits with an amount of 49.2%, followed by spermidine with 29.5% and putrescine with 21.3%. [93] Serotonin, tyramine, histamine, noradrenaline, and tyramine are found in higher amounts in cheese compared to amino acids due to the fermentative-activities of bacteria. [58] In a study on cheese products in Brazil, Vale et al. reported the amount of histamine in cheese as 19.65 mg/100 mg, the amount of phenylethylamine, spermidine, serotonin, agmatine and tryptamine as <10 mg/100 g, cadaverine as 111 mg/100 g, tyramine as 21.25 mg/100 g and putrescine as 17.37 mg/100 g. [90] Another study found putrescine, cadaverine, tryptamine, β-phenylethylamine, serotonin and tyramine in ground Turkish coffee samples and putrescine, cadaverine, tryptamine, β-phenylethylamine, serotonin and tyramine in brewed Turkish coffee samples. It was also demonstrated that both ground and brewed coffee samples had the highest amounts of serotonin. [97]

Similar to other biogenic amines such as histamine and tyramine, serotonin is also of vital importance for the proper functioning of the nervous system and blood pressure control. [98-100] A certain amount of serotonin is stored in thrombocytes in the body, and serotonin release causes vasodilatation in cerebral vessels, which is considered to trigger the formation of migraine attacks along with thrombocyte dysfunction. [22,101] The connection between migraine and serotonin was first raised during the 1950s. [102] In the following years, the relationship between serotonin levels in plasma and migraine attacks was revealed and called the “serotonin hypothesis”. [103,104] It is known that thrombocyte aggregation in migraine patients is easier as a response to vasoactive amines. Amines
such as serotonin and tyramine trigger this aggregation activity. Serotonin levels in plasma may slightly increase during the early stages of migraine attacks, as serotonin release in thrombocytes require aggregation. Thrombocytes in migraine patients contain monoamine oxidase enzyme in lower concentrations between migraine attack intervals. Aggregation is considered to increase during the prodromal phase of migraine, while it decreases during the headache phase.\cite{105,106}

In a study on tryptophane, which is a precursor to serotonin, two different groups consisting of migraine patients and healthy individuals were given an amino acid mixture containing tryptophane and a tryptophane-poor amino acid mixture, respectively, to reduce short term serotonin synthesis. It was found eight hours later that migraine patients who were given a tryptophane-poor amino acid mixture suffered more from sickness, headaches, and brightness- and light-induced headaches compared to healthy individuals. It was also argued that cerebral serotonin synthesis was reduced due to a lack of tryptophane, which contributed to migraine symptoms. In another study on tryptophane, similarly, some measurements were performed seven hours later after the patients consumed a tryptophane-poor amino acid mixture. It was observed again that migraine attacks and vestibulocochlear disorders increased due to a lack of tryptophane and reducing serotonin synthesis.\cite{107}

Fat rich foods cause an increase in the number of plasma thrombocytes and a decrease in plasma serotonin levels, thus resulting in headache attacks.\cite{108} It was also reported that fish species such as morina and somon containing a high level of omega-3 fatty acids prevented migraine attacks. Besides, thanks to the regulatory effect of Omega 3 fatty acids on nervous cells, they are considered to create a resistance mechanism against migraine attacks.\cite{33} As for the relationship between serotonin, estrogen, and migraine, estrogen increases serotonin levels and reduces serotonin reuptake and elimination, which increases a patient’s pain tolerance.\cite{109} Although serotonin intake does not pose a risk in lower amounts, it is known to lead to some toxic effects and a reaction called Serotonin Syndrome (a rare but fatal condition) in individuals with genetic disorders as well as due to the simultaneous use of Monoamine Oxidase Inhibitor (MAOI) and other drugs causing serotonin syndrome.\cite{110}

### Tryptamine and migraine

Biogenic amines are given a name based on an amino acid which is the reason for their formation. Tryptamine is formed by tryptophane.\cite{36} It is a chemically aromatic and heterocyclic amine included in the group of diamines.\cite{110} Different amines such as tryptophane, tyramine and histamine are found in high amounts in cheese due to fermentative functions.\cite{48} In a study on legumes, Shalaby used beans, chickpeas, and lupin to measure their tryptamine levels and found that they contained 30.2 mg/kg, 24.3 mg/kg and 11.7 mg/kg, respectively.\cite{111} Tryptamine, tyramine, cadaverine, putrescine and histamine are found in fermented products.\cite{112} A study reported that tarhana soup, a traditional Turkish soup, contained putrescine, cadaverine, spermidine, spermine, tyramine, histamine and agmatine in varying amounts, while it did not contain any methyamine, β-phenylethylamine and tryptamine.\cite{113} In a similar study, cadaverine, putrescine, tyramine and β-phenylethylamine were not found in durable yoghurt types, while only tryptamine was found in yoghurt samples.\cite{114} Tryptamine is a quality indicator in tomato and tomato products.\cite{115} It was also stated that spermine, spermidine, tyramine and tryptamine increased biological activities of histamine and created a synergistic effect.\cite{79} Histamine, tryptamine, β-phenylethylamine and tyramine are biologically active amines, and they create vasoactive or psychoactive effects on the human body. Psychoactive amines play a role in neural transmitters and affect the nervous system, while vasoactive amines usually affect the vascular system.\cite{116} A tryptamine amount of 10 to 25 mg/kg was reported to cause severe headaches.\cite{36,40}

### Cadaverine, putrescine and migraine

Cadaverine and putrescine are formed by bacterial activities of ornithine amino acids.\cite{116} Putrescine is abundant in various foods such as fruits, cheese and non-green vegetables.\cite{117} The amounts of tyramine, putrescine, histamine and cadaverine in dried fermented sausages in Greece were calculated as 197.7 mg/kg, 96.5 mg/kg, 7.0 mg/kg and 3.6 mg/kg, respectively. In Italy, on the other hand, the amounts of agmatine and spermine in salami samples were measured as 8.3 mg.\cite{118} Another study on sausage samples in Poland demonstrated that total amounts of dominant biogenic amines such as tyramine, putrescine and 2-phenylethylamine were measured as 17.1 mg/kg.\cite{119} Fruit and fruit juices are particularly rich in putrescines.\cite{35,120} Diamines such as putrescine and cadaverine do not directly affect human health.\cite{121,122} Higher diamine concentrations increase the absorption of biogenic amines in intestines and reduce amine catabolism.\cite{123} Also, diamines such as putrescine and cadaverine often increase the toxic effects of histamine and thus contribute to symptoms such as headache and food poisoning.\cite{124} Putrescine and cadaverine (putrefactive amine) increase the toxic effects of tyramine and phenylethylamine. Enzymes that metabolize these biogenic amines interact with different enzymes such as diamine oxidase, monoamine oxidase and histamine methyltransferase to display their effects.\cite{125} They inhibit enzymes (MAO and DAO) in the detoxification system and increase the toxic effects of histamine and other amines such as headache and respiratory distress.\cite{126} It is known that biogenic amines in beer contribute to headache attacks in migraine patients. However, their effects vary from one patient to another. Izquierdo-Pulido et al. reported that agmatine and putrescine were found in all beer types.\cite{127} 2000 ppm of cadaverine, tyramine and putrescine did not display any negative effects on migraine patients. Therefore, acute toxicity levels for tyramine and cadaverine were specified as more than 2000 ppm.\cite{112,128}

### Polyamines and migraine

Amines such as spermine and spermidine, which are also known as polyamines, play important roles in the human body.\cite{129} Polyamines contribute to various mechanisms in the human body such as cell tissue regeneration, organ development, immune system and neurotransmitters in the nervous system.\cite{129,130} Polyamines are responsible for RNA, DNA and protein synthesis in the human body. In addition to being produced endogenously, they can be also consumed exogenously in a diet.\cite{31}
Polyamines such as spermidine and spermine are biological amines that are formed naturally in foods. However, their formations are not correlated with bacteriosis. [80] Spermine and spermidine are among the most common amine groups in nutritional elements. [11] Zhai et al. found eight biogenic amines in 13 different fish species among 49 fish species in South China (histamine, tryptamine, putrescine, phenylethylamine, cadaverine, spermine and spermidine). [12] Spermidine, histamine, putrescine and cadaverine are important quality indicators for fish and fish products. [13] In Czech Republic, 112 raw samples obtained from freshwater fish, saltwater fish and other sea creatures used in restaurants were found to contain high amounts of biogenic amines. [14] The most common biogenic amines in fresh fruit and vegetables and fermented products are spermine, spermidine, putrescine and tyramine. [83]

Although various biogenic amines in different structures are needed for the proper functioning of the human body and health, the consumption of foods containing a high amount of biogenic amine may result in some toxic effects. [135] For instance, spermine and spermidine increase the toxic effects of tyramine, histamine and phenylethylamine. Enzymes that metabolize these biogenic amines also interact with different enzymes such as diamine oxidase, monoamine oxidase and histamine methyltransferase, which cause various problems in the human body such as headache, respiratory distress and food poisoning. [124,125] (values for oral toxicity values in spermine and spermidine were calculated as 600 ppm. [128]

Nitrosamine and migraine

Nitrosamines are usually formed by reactions of secondary and tertiary amines with nitrite under certain conditions. [136] The existences of secondary and tertiary amines such as Dimethylamine (DA) and Trimethylamine (TMA) are effective in the formation of nitrosamine. Putrescine and cadaverine are transformed into secondary amines such as pyrroline and piperidine thanks to the heat. Pyrroline and piperidine can form cancerogenic nitrosamines through their reactions with nitrite, which may occur in an acidic, neutral, and basic environment. Nitrite is necessary for the formation of nitrosamine reaction. [136,137] Nitrosamines are cancerogenic amines. [138] Nitrate degradation in saliva or intestinal bacterial can trigger nitrite formation. [57] Nitrate intake occurs through the consumption of processed foods such as beef, lettuce, celery, spinach, cauliflower, and potato. [31,139] Processed meat products (salam, fermented sausage, and sausage) create nitrates, nitrates and cancerogenic nitrosamines (E250, E251). Individuals who consume sausage and other dried meat and fish products may suffer from head attacks within several minutes. Metmyoglobin is formed by nitric oxygen release, reducing blood oxygen-carrying capacity. As a result, vasodilatory effects contribute to skin redness, headaches, and neck aches. [117] Fukui et al. reported that sausage and salami were triggering factors for migraine patients by 6% and 4.5%, respectively. [139]

Conclusion

Migraine is a polygenic disease that affects an individual’s life negatively. Different theories have been so far proposed regarding migraine attacks. However, more studies are needed to reveal various migraine triggering factors in different patients. It is widely known that most of these factors is usually food-related factors that contain chemicals with biogenic amines. Until today, in different hypotheses, biogenic amines such as histamine, tyramine, phenylethylamine, and serotonin were held responsible for migraine attacks. Other amines too affect these amines and play a role in migraine attacks. Therefore, more studies must be carried out to explore the relationship between migraine and biogenic amines.

Conflict of Interests

The authors declare that they have no conflict of interest.

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