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Biochemical and Pharmacological Properties of Biogenic Amines

Dincer Erdag, Oguz Merhan and Baris Yildiz

Abstract

Biogenic amines are low molecular weight organic nitrogen compounds. They are formed by the decarboxylation of amino acids or by amination and transamination of aldehydes and ketones during normal metabolic processes in living cells and therefore are ubiquitous in animals, plants, microorganisms, and humans. In food and beverages, they are formed by the enzymes of raw materials or are generated by microbial decarboxylation of amino acids. The structure of a biogenic amine can be aromatic and heterocyclic amines (histamine, tryptamine, tyramine, phenylethylamine, and serotonin); aliphatic di-, tri-, and polyamines (putrescine, cadaverine, spermine, spermidine, and agmatine); and aliphatic volatile amines (ethylamine, methylamine, isopentylamine, and ethanolamine). Many of them possess a strong pharmacologic effect, and others are important as precursors of hormones and components of coenzymes. The biogenic amine intoxication leads to toxicological risks and health hazards that trigger psychoactive, vasoactive, and hypertensive effects resulting from consumption of high amounts of biogenic amines in foods. The toxicological effects of biogenic amines increase when the mono- and diaminoxidase enzymes are deficient or drugs that inhibit these enzymes (pain reliever, stress, and depression drugs) are used. In this chapter, biosynthesis of biogenic amines, their toxic effects as well as their physiological functions, and their effect on health will be described.

Keywords: biochemistry, biogenic amines, health, pharmacology, toxicity

1. Introduction

Biogenic amines found in animals, plants, microorganisms, and humans are formed by the decarboxylation of amino acids or amination and transamination of aldehydes and ketones during the standard metabolic processes.

Biogenic amines, having several critical biological roles in the body, have essential physiological functions such as the regulation of growth and blood pressure and control of the nerve conduction. Besides, they are required in the immunologic system of intestines and in maintaining the activity of the standard metabolic functions, and when taking the nourishment in high concentrations, they cause disorders in nervous, respiratory, and cardiovascular systems and allergic reactions as well. In this chapter, biosynthesis of biogenic amines, their toxic effects as well as their physiological functions, and their effect on health will be presented.

2. Biogenic amines

2.1 Decarboxylation of amino acids

CO₂ and biogenic amine occur as a result of the enzymatic reaction catalyzed by pyridoxal phosphate to decarboxylate the amino acid (**Figure 1**) [1]. Biogenic amines are biologically active molecules, as they are formed by decarboxylation of amino acids or amination and transamination of aldehydes and ketones during standard metabolic processes [2]. Biogenic amines take charge of the proliferation and differentiation of cells and their metabolism by entering into the structure of hormones, cobalamin (vitamin and aminoacetone), and coenzyme A in the body [3]. They have importance regarding the environment by causing water pollution, as their formations pertain to the amino acid and microorganisms [3, 4]. Biogenic amines may cause intoxications when taken in high amounts [5].

2.2 Classification of the biogenic amines

Biogenic amines are organic nitrogen compounds having a low molecular weight [5, 6]. Their chemical structure can be classified as (i) aromatic and heterocyclic (histamine, tryptamine, tyramine, phenylethylamine, and serotonin); (ii) aliphatic di-, tri-, and polyamines (putrescine, cadaverine, spermine, spermidine, and agmatine); and (iii) aliphatic volatile amines (ethylamine, methylamine, isopentylamine, and ethanolamine) (**Figure 2**) [7, 8]. Besides, their amine group classifications include (i) monoamine (phenylethylamine, tyramine, methylamine, ethylamine, isopentylamine, and ethanolamine), (ii) diamine (histamine, tryptamine, serotonin, putrescine, and cadaverine), and (iii) polyamine (spermine, spermidine, and agmatine) [7–9].

2.3 Biosynthesis and functions

Biogenic amines generally occur as a result of free amino acid decarboxylations with the microbial enzymes. Amino acid decarboxylation happens by removal of the α-carboxyl group [10]. Their occurrences are as below: histamine from histidine amino acid, tyramine from tyrosine amino acid, tryptamine and serotonin from tryptophan amino acid, phenylethylamine from phenylalanine amino acid, putrescine from ornithine amino acid, cadaverine from lysine amino acid, and agmatine from arginine amino acid (**Figure 3**) [11–13].

Biogenic amines play an essential role in cell membrane stabilization, immune functions, and prevention of chronic diseases, as they participate in the nucleic acid and protein synthesis [14]. Besides, they are compounds created as the growth regulation (spermine, spermidine, and cadaverine), neural transmission (serotonin), and inflammation mediators (histamine and tyramine) [6, 15].

Histamine, a standard component of the body, consists of histidine amino acid as a result of histidine decarboxylase activity depending on pyridoxal phosphate

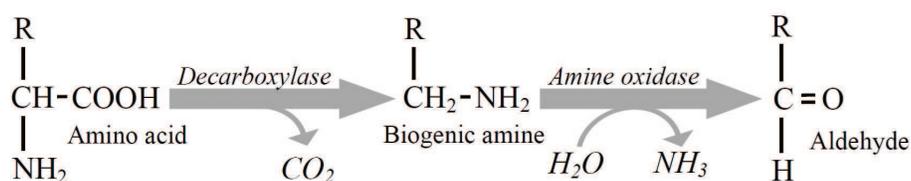


Figure 1.
Decarboxylation of amino acids.

(**Figure 3**) [16]. Histamine distribution and concentration found in the tissues of all vertebrates are very unsteady [17, 18]. Histamine takes charge of some functions related to balancing the body temperature and regulating the stomach volume, stomach pH, and cerebral activities [19] as it participates in the essential functions such as neurotransmission and vascular permeability [20, 21]. However, it also plays a role in starting the allergic reactions [22, 23].

Tryptamine consists of tryptophan amino acid as a result of the aromatic L-amino acid decarboxylase activity (**Figure 3**) [24, 25]. Tryptamine is a monoamine alkaloid found in plants, fungi, and animals [26]. Tryptamine, found in trace amounts in mammalian brains, increases blood pressure [10, 27] as well as plays a role as a neurotransmitter or neuromodulator [26].

The amino acid of phenylalanine synthesizes phenylethylamine through the aromatic L-amino acid decarboxylase in humans, some fungi, and bacteria as well as several plants and animal species (**Figure 3**) [28–30]. It functions as a neurotransmitter in the human central nervous system [31, 32].

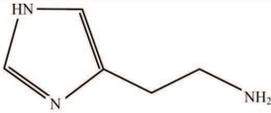
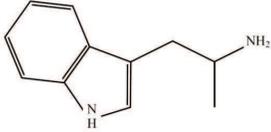
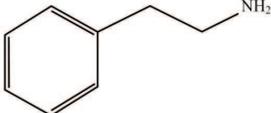
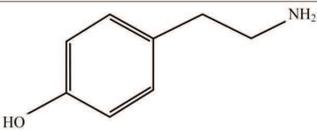
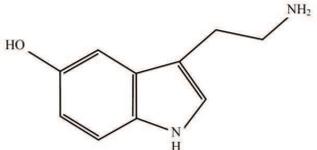
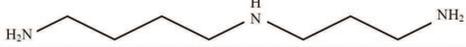
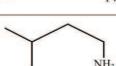
| Classified Chemical Structures | | |
|------------------------------------|------------------|--|
| Aromatic and Heterocyclic Amines | Histamine |  |
| | Tryptamine |  |
| | Phenylethylamine |  |
| | Tyramine |  |
| | Serotonin |  |
| Aliphatic Di-, Tri- and Polyamines | Putrescine |  |
| | Cadaverine |  |
| | Spermidine |  |
| | Spermine |  |
| | Agmatine |  |
| Volatile Aliphatic Amines | Methylamine |  |
| | Ethylamine |  |
| | Isopentylamine |  |
| | Ethanolamine |  |

Figure 2.
 Classification of biogenic amines according to their chemical structures.

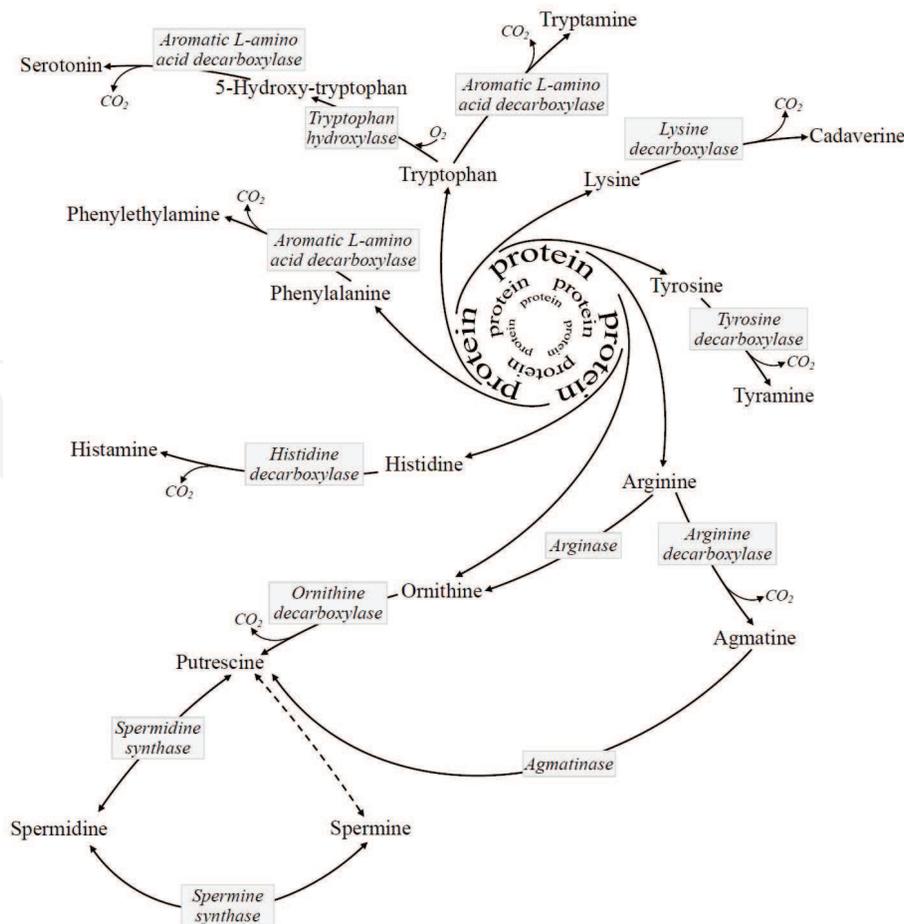


Figure 3.
Formation mechanism of biogenic amines.

Tyramine, consisting of tyrosine amino acid as a result of tyrosine decarboxylase activity, is generally found in low amounts (**Figure 3**) [33–36]. Tyramine leads to several physiological reactions such as blood pressure increase, vasoconstriction [37], tyramine active noradrenalin secretion, etc., as the sympathetic nervous system controls several functions of the body [38, 39]. Tyramine, stored in the neurons, causes the increase in the tear, salivation and respiratory as well as mydriasis [39].

Tryptophan synthesizes serotonin as a result of tryptophan hydroxylase and aromatic L-amino acid decarboxylase enzyme activities (**Figure 3**) [11, 40]. Serotonin, one of the crucial neurotransmitters of the central nervous system, plays a role in plenty of critical physiological mechanisms such as sleep, mood disorders, appetite regulation, sexual behavior, cerebral blood flow regulation, and blood-brain barrier permeability [41, 42].

Putrescine consists of ornithine amino acid as a result of ornithine decarboxylase activity. Besides, it may be synthesized by arginine through the agmatine and carbamoylputrescine (**Figure 3**) [12, 39, 43, 44]. Putrescine, produced by bacteria and fungi, contributes to the cell growth, cell division, and tumorigenesis [45, 46] as it is the preliminary substance of spermidine and spermine [12, 47].

Cadaverine, synthesized by lysine as a result of lysine decarboxylase enzyme activity, takes charge of the diamine and polyamine formations (**Figure 3**) [45, 48, 49].

Spermidine synthase catalyzes spermidine formation from putrescine (**Figure 3**) [50, 51]. Spermidine is a precursor of other polyamines such as spermine and structural isomer thermospermine [45, 52]. Spermidine, regulating several crucial biological processes ($\text{Na}^+ - \text{K}^+$ ATPase), protects the membrane potential and controls the intracellular pH and volume [53]. Besides, spermidine, a polyamine found in the cellular

metabolism, has a role in the neuronal nitric oxide synthase inhibitions and intestinal tissue developments [54].

Spermine, whose precursor amino acid is ornithine, is formed from spermidine through the spermine synthase enzyme (**Figure 3**) [51]. Spermine is present in several organisms and tissues, as it is a polyamine that is found in all eukaryotic cells and has a role in the cellular metabolism [52, 55]. It plays a role in the intestinal tissue developments and stabilizes the helical structure in viruses [52, 56, 57].

Agmatine is a biogenic amine formed by arginine decarboxylase enzyme activity of arginine amino acid (**Figure 3**) [12, 44, 58]. Agmatine participates in the polyamine metabolism over the putrescine hydrolyzed by the agmatine enzyme and has several functions such as nitric oxide synthesis regulation, polyamine metabolism, and matrix metalloproteinase and enzyme activity leading to H₂O₂ production [59, 60].

The detoxification system, splitting the biogenic amines in the human body, consists of monoamine oxidase (MAO), diamine oxidase (DAO), polyamine oxidase (PAO), and histamine-N-methyl transferase (HNMT) [17, 61, 62].

3. Effect of biogenic amines on health

Biogenic amines have several important biological roles in the body and constitute the first step of protein, hormone, and nucleic acid synthesis [61, 63]. The polyamines such as putrescine, spermine, and spermidine are the unique components of living cells. Besides, the polyamines were stated to require maintaining the intestinal immunologic systems and healthy metabolic function activities [52, 64–67]. The biogenic amines cause respiratory disorders, headache, tachycardia, hypo- or hypertension, and allergic reactions when taken in high concentrations together with nutrients [68].

Biogenic amines are vasoactive components, and taking them in high amounts leads to change in blood pressure in humans and animals. The amines bear essential psychoactive or vasoactive effects, as they have the biological activities such as histamine, tryptamine, tyramine, and phenylethylamine [33]. Histamine is a biologically active amine and quickly scatters to the tissues through blood circulation and leads to several reactions. However, in the case where aminoxidase enzyme inhibitors are present in the environment, the biogenic amine prevents detoxification, and health problems (erythema, edema, rash, headache, burning, etc.) show up [17, 68]. Histamine also has essential metabolic functions such as a role in the nervous system functions and blood pressure control. It mainly takes effect by binding to the cardiovascular system (vasodilatation and hypotension) and cell membrane receptors in several secretory glands (such as gastric acid secretion) [22, 23]. In addition to them, it may lead to some neurotransmission disorders and causes headache, flushing, gastrointestinal disorders, and edema by giving rise to blood vessel dilatations [61, 69]. Histamine intoxicates when orally taken in amounts of 8 mg and above [3]. Individuals generally have lower intestinal oxidase enzyme activities according to the healthy persons, as they hold the gastrointestinal problems such as gastritis, stomach and colonic ulcers [6, 69].

Intestinal mucosal injuries may decrease the enzyme functions by detoxifying the biogenic amines [17, 63]. The DAO activity disruption causes histamine intolerance and also allergic reactions as a result of the drug utilization, as it is caused by genetic and gastrointestinal diseases or DAO inhibition [17, 70]. It was found to increase the histamine toxicity by preventing the histamine oxidation of putrescine, cadaverine, and agmatine in humans [71].

Biogenic amines lead to hypertension, as they have vasoconstriction effects such as tyramine, phenylethylamine, and tryptamine [37, 68, 72]. Consuming tyramine-rich nutriment was found to react with the tyramine MAO inhibitor drugs and cause hypertensive crisis and also migraine in some patients [73]. Tyramine is revealed to inhibit MAO, tryptamine DAO, phenylethylamine DAO, and HNMT enzymes [74, 75].

In the case of deficiency of putrescine, found in the high concentration in brains, is stated to develop the depression and also useful in the depression physiopathology [3, 76].

The pharmacological effects of putrescine, cadaverine, spermine, and spermidine are at lower levels according to histamine, tyramine, and phenylethylamine [77]. Putrescine, causing hypotension, bradycardia, and lockjaw, creates carcinogenic heterocyclic compounds including nitrosamine, nitrosopyrrolidine, and nitrosopiperidine as some biogenic amines such as cadaverine, spermine, and spermidine react with the nitrite [5, 10, 39, 78].

Polyamines are known to lead to low-dose colon cancer by affecting the cell developments and differentiation [79, 80]. In addition to them, putrescine, cadaverine, spermine, and spermidine were also found to induce apoptosis and inhibit cell proliferation. The high-dose putrescine was found to induce apoptosis and prevent the spread [81, 82]. This putrescine effect pertains to increasing the nitric oxide synthesis, inhibiting the redox reactions and binding directly to the carcinogenic agents [82].

Eating disorders such as anorexia nervosa and bulimia nervosa disrupt the function of brain serotonin [83]. Albumin deficiency shows up due to inadequate nutrition, and tryptophan transition from the blood-brain barrier increases, as it could not connect to the albumin. As a consequence, an increase occurs in the brain serotonin concentration [84, 85]. The drugs (MAO inhibitors) are used, as they change the serotonin levels in the depression, generalized anxiety disorder, and social phobia treatments [86]. The MAO inhibitors, used in treating these diseases, increase the brain concentrations by preventing the neurotransmitter (serotonin) disruptions [73, 86].

Agmatine shows a nephroprotective effect by increasing the glomerular filtration rate, and it also has a hypoglycemic impact as a result of several molecular mechanisms taking place in the blood glucose regulation [56, 87]. Besides, the agmatine level of schizophrenia patients was shown to be higher compared to that of healthy humans [88].

4. Conclusion

The present information related to biogenic amines having different physiological functions and similar chemical structures and metabolic pathways was updated, undesirable effects were considered more comprehensively for human and animal health, and information was submitted about the essential diseases caused by biogenic amines.

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