REVIEWS

Review article
https://doi.org/10.36233/0372-9311-230

The role of cyanotoxins in human and animal pathology (a review)

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Abstract
Cyanobacteria are the oldest and most widespread form of life on Earth. Many of them produce toxins that are dangerous to humans and animals. The review presents data on the distribution of toxin-producing cyanobacteria, the pathogenesis of the action of toxins on human and animal cells and tissues. A significant consideration is given to the neurotoxic effect of cyanotoxins, which is most common cause of animal death. Cyanotoxins can cause severe damage to the central and peripheral nervous systems, as well as the liver, kidneys, reproductive system and digestive tract. Data on hepatotoxic, nephrotoxic, cardiotoxic, immunotoxic effects of cyanotoxins are presented. Their role in the human brain degenerative diseases is considered. The possible influence of cyanotoxins on carcinogenesis, especially in the liver, large intestine and rectum, is evaluated. The limitations of the existing data on the pathogenicity of cyanobacteria and medical care necessary for cyanotoxin-induced diseases are noted. The necessity for further studies of clinical manifestations of pathological processes caused by cyanotoxins, the development of diagnostic methods and specific therapy of poisoning is discussed.

Keywords: *cyanobacteria, microcystins, cylindrospermopsins, anatoxins, saxitoxins, cyanotoxin neurotoxicity, cyanotoxin hepatotoxicity*

Funding source. This work was financially supported by the Ministry of Science and Higher Education of the Russian Federation (research topic No FFZF-2022-0011).

Conflict of interest. The authors declare no apparent or potential conflicts of interest related to the publication of this article.

For citation: Polyak Yu.M., Polyak M.S. The role of cyanotoxins in human and animal pathology (a review). *Journal of microbiology, epidemiology and immunobiology = Zhurnal mikrobiologii, èpidemiologii i immunobiologii.* 2022;99(2): 231–243. DOI: https://doi.org/10.36233/0372-9311-230

Научный обзор
https://doi.org/10.36233/0372-9311-230

Роль цианотоксинов в патологии человека и животных (обзор)

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Аннотация
Цианобактерии (ЦБ) являются древнейшей и широко распространённой формой жизни на Земле. Некоторые представители этих микроорганизмов образуют токсины, опасные для человека и животных. В работе приводятся данные о распространении токсинообразующих ЦБ, патогенезе действия токсинов на клетки и ткани человека, сельскохозяйственных, домашних и диких животных. Уделено серьёзное внимание нейротоксическому действию цианотоксинов (ЦТ), наиболее часто являющихся причиной гибели животных. ЦТ способны вызывать тяжёлые поражения центральной и периферической нервной системы, печени,

почек, репродуктивной системы и пищеварительного тракта. Приводятся данные о гепатотоксическом, нефротоксическом, кардиотоксическом, иммунотоксическом действии ЦТ. Рассматривается их роль в возникновении тяжёлых дегенеративных процессов в мозге человека. Оценивается возможность влияния ЦТ на канцерогенез, особенно в печени, толстом кишечнике и прямой кишке. Отмечена ограниченность существующих данных о болезнетворности ЦБ и той помощи, которая необходима при вызванных ими поражениях. Обсуждается необходимость дальнейших исследований клинических проявлений патологических процессов, вызванных ЦТ, разработки методов диагностики и специфической терапии отравлений.

Ключевые слова: *цианобактерии, микроцистины, цилиндроспермопсины, анатоксины, сакситоксины, нейротоксичность цианотоксинов, гепатотоксичность цианотоксинов*

Источник финансирования. Работа выполнена в рамках государственного задания при поддержке Минобрнауки России по теме FFZF-2022-0011.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Для цитирования: Поляк Ю.М., Поляк М.С. Роль цианотоксинов в патологии человека и животных (обзор). *Журнал микробиологии, эпидемиологии и иммунобиологии.* 2022;99(2):231–243.
DOI: https://doi.org/10.36233/0372-9311-230

Introduction

Cyanobacteria are the oldest living organisms on Earth. There is no doubt that they existed on the planet in the Proterozoic, and at the very beginning of this period. However, there is strong evidence that they lived earlier in the Archean, which is the oldest period of the existence of the Earth [1, 2]. Evidence is stromatolites, fossils of cyanobacterial communities, and natural mats better known to medical microbiologists as biofilms. Their structure is specific and typical for these microorganisms. Therefore, it can be assumed that cyanobacteria have existed for about 3 to 3.5 billion years. The conditions in which they lived and multiplied at that time were more than severe: sharp temperature changes, moisture deficiency, oxygen-free environment, earthquakes, etc. This indicates the high resilience of cyanobacteria, their ability to adapt to adverse environmental conditions. This is confirmed today since cyanobacteria are found not only in the aquatic environment (their favourite habitat) but also in the desert, on rocks, and in the Arctic regions [2–4]. It is appropriate to recall that cyanobacteria inhabited the Earth when there was no oxygen in the atmosphere. One can claim that they played a significant (if not decisive) role in the formation of the atmosphere, primarily due to oxygen saturation. It is predicted that warming will result in further distribution of cyanobacteria [5].

In previous years' publications, cyanobacteria are called blue-green algae. Indeed, initially they were referred to as eukaryotic algae. For the first time, Cohn pointed out their belonging to prokaryotes in the middle of the nineteenth century based on the study of cell morphology. Later, several studies confirmed that blue-green algae were microorganisms. It should be noted that Russian scientists made a valuable contribution to determining the nature of cyanobacteria [6]. However, the term "blue-green algae" often appears until now not only in popular literature but also in scientific literature, which is, strictly speaking, incorrect.

In this article, it is not possible to discuss the complex problems related to the taxonomy of this broad group of microorganisms and their metabolism. In addition, they have not been fully resolved. It is important to note that cyanobacteria are phototrophs, and light is their main source of energy. Therefore, they cannot exist in human and animal organisms. Hence, an important requirement for understanding their pathogenicity is that the danger to humans and animals is not the cyanobacteria themselves. The danger is posed by the toxic products that cyanobacteria exude into the environment [7]. Toxins are the cause of acute and chronic pathologies in humans and animals. These poisonings often become deadly, as evidenced by numerous reports of deaths of domestic, agricultural, and wild animals [8]. This review discusses the main types of cyanotoxins, their distribution, ways of entry into human and animal organisms, and the nature of toxic effects.

Classification of cyanotoxins

Not all cyanobacteria produce toxins. Toxin producers are members of the genera *Microcystis, Nodularia, Dolichospermum (Anabaena), Nostoc, Cylindrospermopsis, Lyngbya,* and several others [7]. In the scientific literature in recent years, the genus *Anabaena* appears among the most frequent representatives of toxin-producing cyanobacteria. Today, the toxin-producing members of this genus are assigned to the genus *Dolichospermum*. Producers of not one, but several toxic substances are common among cyanobacteria. These include the members of the already mentioned genera *Dolichospermum (Anabaena)*, *Cylindrospermopsis, Lyngbya*, and some others.

Cyanobacterial toxins have different chemical structures. Predominantly, they are polypeptides and alkaloids. In addition, some strains have toxic effects due to lipopolysaccharides (LPS). Among the most common and studied toxins are cyclic polypeptides – microcystins and nodularins, and alkaloids – cylindrospermopsins, anatoxins, and saxitoxins [7, 8, 9, 10].

The classification of cyanotoxins by their effect on certain tissues in humans and animals has become widespread [11]. There are hepatotoxic compounds

(microcystins, nodularins), neurotoxic (anatoxin-a, anatoxin-a(s), saxitoxins), and cellular poisons (cylindrospermopsins, LPS). However, this division is very conditional. In fact, most toxins act on several targets directly or indirectly. They can primarily include microcystins, nodularins, and LPS. This is the reason for the frequent mention of the same cardiotoxic, nephrotoxic, dermatotoxic, and immunotoxic products produced by cyanobacteria. In recent years, the effect of cyanotoxins on the reproductive system has attracted researchers' attention. This effect is caused by toxins that belong to different groups according to the selectivity of the action. For example, microcystin-LR negatively affects the structure and function of the ovaries, prostate, placenta, and other organs of animals, which leads to a decrease in their fertility [12].

Mechanisms of toxic action

The structural peculiarities of cyanotoxins and, as a consequence, the selectivity of their action on human and animal tissues are associated with the diverse pathogenesis of the caused disorders. The effect of toxins has common features and is specific at the same time. The pathophysiology of the processes caused by many cyanotoxins has not been sufficiently studied. The greatest attention is paid to the effect of microcystins [13, 14]. The changes caused by these toxins more or less correspond to the pathogenesis of processes caused by some toxins (nodularins, cylindrospermopsins).

Oxidative stress is a fairly well-established cause of pathological changes, which, in certain concentrations, are caused by microcystins and, more likely, other cyanotoxins. It is believed to develop due to the formation of reactive oxygen species (active radicals) under the action of toxins, as well as disruption of glutathione homeostasis [11, 15].

It is considered that reactive oxygen species (superoxide anion, singlet oxygen, hydrogen peroxide, hydroxyl anion) are formed due to destructive processes in tissues caused by cyanotoxins. These processes involve changes in the pH and redox potential of the medium and suppression of the activity of superoxide dismutase and catalase. In turn, active radicals destroy the structure of cells and, among other things, act on mitochondria, the cell skeleton, and nucleic acids. Changes in mitochondrial membranes are claimed to occur due to the direct action of microcystins.

In the pathogenesis of damage caused by microcystins, much attention is paid to their inhibitory effect on phosphatases (protein phosphatase 1 and protein phosphatase 2A). They are commonly called protein phosphatases PP1 and PP2 [11, 16]. The suppressive effect of toxins has been examined both *in vitro* and in animal studies. Phosphatases play an important regulatory role in cell life, including proliferation, division, and expression of the corresponding genes. PP2A, in addition, suppresses the process of malignant cell degeneration. The suppression of phosphatase activity by microcystins leads to the accumulation of phosphorylated products, disruption of cell viability, and cell death [11].

The pathogenesis of the neurotoxic effect of cyanotoxins is multivariate. Microcystins can cross the blood-brain barrier and cause brain dysfunction due to the induction of oxidative stress and inhibition of cellular phosphatase activity. However, the violation of interneuronal and neuromuscular transmission by neurotoxins (saxitoxins, anatoxin-a, and kalkitoxin) due to the inhibition of acetylcholinesterase activity and the impaired function of ion channels has been studied more and highlighted in the scientific literature. Both channel inactivation (saxitoxin) and activation (anatoxin-a) have been studied. It is believed that beta-N-methylamino-L-alanine (better known by the abbreviation BMAA) produced by cyanobacteria has a special mechanism of action on the brain. BMAA causes degeneration of nervous tissue that leads to severe pathology – amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, and dementia [17].

A special place in the pathogenesis of diseases caused by cyanobacterial toxins belongs to their combined effect. Cyanobacteria usually form associations. Toxic products of different cyanobacteria can exert combined and even potentiating effect [18]. The same applies to the combination of cyanotoxins with toxins of other origins [19].

Cyanotoxin poisoning of animals and humans

Cyanotoxin poisoning of animals, usually fatal, has been recorded in Europe, North and South America, Asia, and Australia. The lesions were generally associated with drinking water [20, 21, 22]. The death was observed among representatives of wild fauna (elephants, antelopes, flamingos, and many others), farm and domestic animals (cattle, horses, dogs, etc.). Many of these incidents are documented in scientific literature and media publications. Presumably, the first such report was published in Poland in the 19th century [23]. For obvious reasons, it is not necessary to state that cyanobacteria were the cause of animal death. However, the description of the death of cattle corresponds to the current understanding of cyanotoxin poisoning.

The epidemiology of human lesions seems to be more complex [24]. Acute and chronic diseases are associated with cyanotoxins, and the latter cause discussions with contradictory statements. The number of known deaths due to acute human cyanotoxin poisoning is small. Non-fatal pathologies of the gastrointestinal tract, skin, and respiratory tract are more common. Such poisoning has been recorded on almost all continents except Antarctica. The number of observations is the largest in the countries in which microbiological control is carried out, and it is possible to confirm the etiology of the disease through microbiological and

JOURNAL OF MICROBIOLOGY, EPIDEMIOLOGY AND IMMUNOBIOLOGY. 2022; 99(2)
DOI: https://doi.org/10.36233/0372-9311-230
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toxicological studies. These include many European countries, the USA, Canada, China, Brazil, and some others.

The causes of acute human poisoning are diverse. Among them are drinking water and food containing cyanotoxins [25, 26]. Cyanotoxins enter the human body not only with drinking water. A person comes into contact with cyanotoxins when doing water sports, relaxing on the shore of reservoirs, or bathing in water containing cyanotoxins. Upon contact, various lesions are observed in the skin, respiratory tract, and mucous membranes of the eyes [27, 28]. Rarely, the source of poisoning can be meat obtained from animals that have consumed contaminated food. The emphasis, however, is on drinking water and contact with water during sports and recreation [29, 30]. A special place in the description of acute poisoning should be given to unique observations of the consequences of intravenous injection of solutions containing cyanotoxins into patients. This incident will be discussed in more detail later.

It is difficult to judge the epidemiology of human chronic lesions. Especially, since the role of cyanotoxins in the origin of cancer and severe brain pathologies (Parkinson's disease, Alzheimer's disease, and some others) is recognised by some researchers and disputed by others.

Neurotoxicity of cyanotoxins

Cyanobacterial neurotoxins are associated with frequent and quite severe, including fatal, pathology in humans and, especially, animals. Numerous reports of mass deaths of farm animals, pets, and wild animals are usually considered the results of drinking water that contained cyanobacteria producing neuroparalytic poisons [16, 31, 32]. Without exaggeration, this is the main information about cyanobacteria.

The human health effects caused by cyanobacterial neurotoxins are conditionally divided into two groups. Some of them are acute. They are usually the result of violations of synaptic transmission in the interneuronal and neuromuscular synapses. As a rule, neurotoxins cause a synapse blockade, which leads to muscle paralysis with respiratory disorders [16]. The second group of pathologies is determined by the penetration of cyanotoxins through the blood-brain barrier into the brain, deposition in its tissues, and the development of degenerative processes in this organ. Such processes develop gradually and can lead to severe neuropsychiatric disorders [33]. Acute lesions of the nervous system of the first group, their etiopathogenesis and symptoms are beyond doubt. They have been repeatedly demonstrated *in vitro*, in experiments, and in clinical settings (less in medical, more in veterinary practice). Meanwhile, chronic brain diseases remain debatable.

Many toxins produced by cyanobacteria have a neurotropic effect. For some of them, including saxitoxins, anatoxin-a, homoanatoxin-a, anatoxin-a(s), antillatoxin, BMAA, and some others, the main target of damaging effect is the nervous system. Another group of toxic substances (microcystins, nodularins, and cylindrospermopsins) exhibit multiple toxic effects. Their targets are many tissues, including the brain and the peripheral nervous system. However, in classifications, they are more often referred to other groups (hepatotoxins, cytotoxins, etc.) [31, 34].

Saxitoxins belong to cyanotoxins that are unanimously classified as neurotoxins. Many representatives of cyanobacteria produce saxitoxin including those from the genera *Dolichospermum (Anabaena), Cylindrospermopsis, Lyngbya*, etc. The greater the biomass of the producing microorganism, the more intense the cell lysis, the higher the concentration of saxitoxins, and the more dangerous the product containing cyanobacteria. Most often, a high concentration of toxins is found in water, but they are found both in food and in air containing drops of moisture. Saxitoxin is well absorbed from the intestine, penetrates into a variety of tissues, and, what is especially important in this case, into the nervous system, including the brain [35].

Poisoning of people with saxitoxins is sporadic. However, limited data suggest the possibility of acute poisoning [29]. Descriptions of poisoning symptoms given in the scientific literature are considered the results of damage to the peripheral and central nervous systems. The disease is more severe if the amount of saxitoxin is high.

Under experimental conditions, at farms, and in nature, the death of animals is caused by respiratory failure up to apnea. Suppression of the function of the energy-dependent sodium channels of the neuron axons of peripheral nerve cells leads to disorders of neuromuscular transmission followed by paralysis of the respiratory muscles and respiratory arrest [32, 36].

Anatoxin-a is also unanimously attributed to neurotoxic products produced by cyanobacteria [32]. Its producers are representatives of the genera *Dolichospermum,* (formerly *Anabaena), Cylindrospermopsis*, etc. The damaging effect of the toxin on humans and animals is related to its binding to nicotine acetylcholine receptors of nerve and muscle cells. It leads to a disorder of the effectiveness of synaptic transmission in both interneuronal and neuromuscular synapses.

The main cause of poisoning with anatoxin-a is the use of water containing this toxin. In addition, anatoxin-a can be found in consumed fish, shellfish, and aquatic plants. Anatoxin-a is rapidly absorbed from the intestine and penetrates into the blood and tissues (liver, kidneys, muscles, and others). The toxic effect of anatoxin-a occurs mainly in progressive muscle weakness, which turns into paralysis, including respiratory muscles. There are few examples of human poisoning with anatoxin-a [35]. The fatal poisoning of a man who had respiratory contact with water during cyanobacterial bloom is known. The death occurred from respiratory

paralysis. The effect of anatoxin-a on animals has been studied in more detail including through experimental research.

Another cyanobacterial neurotoxin anatoxin-a(s) is terminologically close to anatoxin-a, although they are two different chemical compounds. The first belongs to organophosphorus compounds and is structurally similar to a number of insecticides. Moreover, it has a certain similarity to sarin (a chemical warfare agent). However, unlike other toxins of a similar structure, anatoxin-a(s) is produced by biosynthesis, and not by chemical synthesis [35, 37]. The producer of anatoxin-a(s) is cyanobacteria of the genus *Dolichospermum* (formerly *Anabaena*).

Anatoxin-a(s) is an irreversible inhibitor of acetylcholinesterase [38]. In experiments with various animals, acetylcholinesterase blockade led to hypersalivation, lacrimation, dysuria, and respiratory arrest. The effect depended on both single and course doses of the toxin. It was found that LD_{50} was 20–50 μg/kg for intraperitoneal injection in mice [37]. The introduction of such doses of anatoxin-a(s) leads to paralysis of the respiratory muscles, which causes the death of animals. There are a limited number of reports of deaths of livestock and wild animals that drank water containing anatoxin-a(s). The death occurred from respiratory paralysis. In clinical practice, atropine is used as an antidote for organophosphate poisoning. It has also been experimentally determined to be effective against anatoxin-a(s).

In recent years, the neurotoxicity of BMAA has attracted special attention. The producers of this toxin are cyanobacteria *Nostoc* and *Dolichospermum* (formerly *Anabaena*). It is also possible that BMAA is produced by other representatives of this group of microorganisms [32, 33]. It is assumed that some aquatic plants and even some species of phytoplankton living in seawater can also produce BMAA. However, the presence of cyanotoxin may be a consequence of secondary accumulation, and the primary producer is cyanobacteria.

BMAA is a non-protein amino acid. The target for its action is the nervous system of humans and animals. It is believed that repeated administration of BMAA over a prolonged time leads to irreversible changes in the central nervous system, which are typical for such human pathologies as Alzheimer's and Parkinson's diseases, and amyotrophic lateral sclerosis. This statement is based on the identification of the mechanism of action of the toxin, experimental studies, and even clinical observations [33, 39]. BMAA enters the human body and animals with food in which the toxin accumulates (plants, marine animals). The toxin penetrates the blood-brain barrier well and is deposited in the brain.

Researchers believe that there are at least several basic mechanisms of the neurodegenerative action of BMAA. An increase in the level of free glutamic acid, as a consequence of the activation of glutamate receptors of nerve cells, is mentioned most often. BMAA is an agonist of glutamate receptors [17, 40]. Excess glutamic acid leads to pathology, which is considered fatal to neurons. Another mechanism is the replacement of the natural amino acid serine with toxic BMAA in the protein molecule formed in neurons. The resulting protein molecule is not capable of folding and spontaneously folds the polypeptide into the spiral inherent in this molecule. BMAA inhibits oxidative stress enzymes, leading to the generation of reactive oxygen species and the destruction of cell structures, including the cell wall, followed by its death. Finally, the toxin is an activator of pro-inflammatory cytokines. In total, all of the above is considered a factor of the death of nerve cells, their apoptosis.

Degenerative changes in the brain, peripheral nervous system, muscle tissue, and retina of the eye were detected in animal experiments, including primates, as well as during autopsy of farm animals that received BMAA in one form or another [40, 41]. The facts of widespread amyotrophic lateral sclerosis and Parkinson's disease among Guam residents are generally cited first as evidence of the possibility of brain nerve tissue lesions. For a long time, the inhabitants of this island intensively used for cooking flour from *Cycas circinalis*. There are a large number of cyanobacteria that produce BMAA in the roots of this plant from the Cycad family. The toxin accumulates in the seeds used for cooking. However, this version is not recognised by all researchers and it is considered appropriate to further accumulate experimental and clinical data on the effect of BMAA on brain nerve tissues [40].

Hepatology

The hepatotoxicity of metabolites produced by cyanobacteria has historically attracted serious attention. It has already been noted that severe fatal lesions in humans are sporadic. However, there is a tragic observation of mass poisoning of people that occurred in Brazil in the last century, when due to violations of the water supply system of the hemodialysis clinic, more than 100 patients were injected intravenously with a solution containing microcystins [42]. Half of the patients died. The drama is known in the literature (including scientific) as the Caruaru syndrome (according to the place of the incident). After hemodialysis, the patients had a headache, muscle weakness, visual impairment, confusion, and a number of other symptoms. At the autopsy, the deceased patients showed mainly changes in the liver, including microscopy. Liver tissue cells were deformed, necrotic changes covered significant areas of the organ. Severe cholestasis was found in the biliary tract. Vacuolisation of the cytoplasm, deformation of the nuclei, and their incomplete division were noted in the hepatocytes themselves. Electron microscopy confirmed deep structural changes in hepatocytes – mitochondria, endoplasmic reticulum, and nuclei.

JOURNAL OF MICROBIOLOGY, EPIDEMIOLOGY AND IMMUNOBIOLOGY. 2022; 99(2)
DOI: https://doi.org/10.36233/0372-9311-230

Several studies carried out in experiments on animals of several species from different habitats that died as a result of drinking water containing cyanotoxins, in general, gave similar results. This indicates a high sensitivity of the liver to the damaging effects of microcystin, nodularin, and cylindrospermopsin [7, 43].

The above hepatology is related to acute lesions. However, the prolonged repeated consumption of small amounts of cyanotoxins also leads to severe liver disease. Cirrhosis and liver cancer are mentioned among them. However, sufficiently convincing statistically confirmed data have not yet been provided [44]. The pathogenesis of liver damage in humans and animals with chronic cyanotoxins entering the body is similar to that given above. This is a lesion of hepatocytes caused by a violation of phosphorylation and destruction of cellular structures, including the apparatus of heredity [11, 45].

Pathology of the cardiovascular system

There is no doubt that cyanotoxins can have a damaging effect on the cardiovascular system (CVS) and blood cells. However, it is emphasised that the pathology of the CVS caused by cyanotoxins has not been adequately studied yet [46]. Experimental studies performed using various animal species and data obtained from *in vitro* experiments confirm the possibility of serious changes in the structure and function of heart tissues, blood vessels, and blood elements when exposed to microcystins (mainly, microcystin-LR) [11, 47, 48]. There are two types of damage: those that arise as a result of the direct action of toxins on the tissue and those that arise as a result of damage to other organs (kidneys, liver, gastrointestinal tract).

As in the other cases mentioned above, the severity of the pathology depends on the concentration of the toxin, the exposure time, and the method of contact of CVS cells and blood with the damaging agent. Targets of toxic action are almost all of the main structures of the CVS (heart, blood, and blood vessels). In particular, serious changes were detected in vascular endothelial cells and cardiomyocytes. The mechanism of action is typical for cyanotoxins: the formation of reactive oxygen species, oxidative stress, destructive processes in the mitochondria of cells, and the cell skeleton. In the myocardial cells, significant changes in the enzymatic pool were revealed, leading to a radical disorder of cell metabolism. Completion of the pathological process is cell death [11, 46]. Necrotic changes in the walls of the arteries contribute to thrombosis.

Blood cells are sensitive to the damaging effect of cyanotoxins (microcystins). Destructive changes were observed in the elements of red and white blood – erythrocytes, lymphocytes, and monocytes.

In vitro and animal experiments have shown that microcystins, even in small amounts, cause endothelium dysplasia of the coronary vessels, restriction of blood flow, and subsequent changes in the myocardium.

As noted above, the effect of cyanotoxins can lead to serious pathology of the liver, kidneys, lungs, and gastrointestinal tract. As a result, indirect morphological and functional damage to the cardiovascular system is possible. In clinical conditions, this issue has not been practically studied, but the occurrence of secondary myocardiopathy, which occurs in diseases of other organs and systems, is well known. Therefore, the relationship between cyanotoxins, damage to internal organs and, as a consequence, the heart, blood vessels, and blood is considered very likely [11].

The effect of cyanotoxins on the immune system

Several experimental studies confidently assert the possibility of a negative effect of cyanotoxins on immunity. According to the authors, cyanobacteria cylindrospermopsins, microcystins and lipopolysaccharides have an immunotoxic effect [48]. However, this list is not final, as evidenced by the not very convincing inclusion of anatoxin-a and BMAA in it in recent years [49, 50].

The ideas about the effect of cyanotoxins on immunity are still mainly based on experimental data. This problem has been studied in a very limited way in humans [48]. The most obvious is damage to cellular immunity. A number of experimental studies indicate that cyanotoxins affect the morphology and function of lymphocytes, plasma cells, and macrophages.

The effect of cyanotoxins on immunocompetent cells can be direct, that is, the result of direct contact, and indirect, due to the destruction of tissues where these cells are deposited. The most obvious sequence of the development of immunotoxic action is the destruction by cyanotoxins of the intestinal wall, in which lymphocytes, plasma cells, and intestinal macrophages are deposited. Destruction of the intestinal mucosa leads to the release and destruction of these cells, which in turn leads to the suppression of cellular immunity both in the intestine and in the body as a whole [48].

The focus on the immunotoxic effect of microcystins reflects a special interest in the damaging effect of this particular group of cyanotoxins [51, 52]. Microcystin-LR is the most frequent research subject, but microcystin-LA is also mentioned among immunotoxic cyanotoxins [51]. Microcystins decrease lymphocyte proliferation, inhibit the activity of natural killer cells, and cause an imbalance in the production and action of cytokines. A special place is occupied by the destruction of the intestinal mucosa by microcystins. As a result, the death of immunocompetent cells and the suppression of the protective reaction of the intestinal wall to microbial invasion and the influence of cyanotoxins occur [48, 53]. Experimental data obtained mainly *in vitro* and *in vivo* in aquatic inhabitants indicate the immunotoxic potential of cylindrospermopsin [48].

The effect of cyanotoxins on humoral immunity is evaluated more carefully. However, destruction of the

intestinal mucosa, suppression of the function of plasma cells, and their destruction, especially in the lamina propria, can limit or even eliminate antibody formation. Blood flow disturbances and vascular thrombosis limit the penetration of serum antibodies (mainly IgG) into the intestinal lumen and its wall. Thus, suppression of humoral immunity as a result of the effect of cyanotoxins seems to be quite possible [48].

Recent experimental studies have established the immunosuppressive effect of anatoxin-a [50], which was previously considered a neurotoxin. Using *Carassius auratus*, it was shown that fish lymphocytes were the target of this cyanotoxin. The reactive oxygen species formed destroy the mitochondria and DNA of the cells. The activity of cellular enzymes and their antioxidant function are suppressed. All this leads to the death of lymphocytes and to the inhibition of their role in maintaining the immune status of the animal. When considering the function of lymphoid cells, both humoral and cellular immunity is reduced.

Another cyanotoxin belonging to the group of neurotoxins that has demonstrated an immunotoxic effect in the experiment is BMAA. At certain concentrations, it changes the morphology and metabolism of monocytes, limits their proliferation, and thereby reduces their phagocytic activity. Since the toxin enters the human body repeatedly with food for a long time, its harmful suppressive effect on the immune system appears to be real [39].

Nephrotoxicity of cyanotoxins

The nephrotoxicity of cyanotoxins is considered a natural result of their penetration into the organ involved in the excretion of these products [54]. It is based mainly on studies of the kidney status in animals that were injected with the toxin in the experiment or drank toxin-containing water [55, 56]. The objects of study of the damaging effect were mainly microcystins. The scientific literature also contains data on the nephrotoxicity of cylindrospermopsin [34].

The mechanism of the nephrotoxic action of microcystins is similar to that already mentioned earlier: suppression of protein phosphatase activity, destruction of the cytoskeleton, and destructive processes in mitochondria and DNA. An obligatory component of the process is the formation of active oxygen radicals. Several clinical observations [54] confirm that microcystins penetrate the kidney tissue, overcome the glomerular barrier, and cause impaired renal function. However, the authors agree that neither experimental nor clinical data are sufficient. Further research is needed. Moreover, the risk of human kidney pathology in the case of microcystin poisoning is considered quite real [54, 57].

Pathologies of the gastrointestinal tract

Since acute poisoning of humans and animals occurs most often when drinking water and eating food containing cyanotoxins, it is natural that the object of their damaging effect is the intestine, usually the mucous membrane [48, 58]. A greater destructive effect is also possible, up to a total wall injury [48]. Enterotoxic cyanotoxins include microcystins, cylindrospermopsins, anabaenolysins, limnothrixin, and some others. In many cases, the statement about their damaging effect is based on experimental data. However, the pathology of the mucous membrane of the small intestine caused by microcystins has clinical confirmation [48, 59].

Symptom complexes usually manifest themselves in a violation of the two main functions of the intestine – suction and secretory with the corresponding clinical manifestations. Intestinal lesions are often accompanied by complications: glossitis, stomatitis, and esophagitis. With prolonged processes, secondary changes occur associated with iron deficiency (anemia), vitamin deficiency, and dysbiosis. Violation of the immune system due to the death of immunocompetent cells concentrated in the intestinal membrane attracts serious attention. The variety of pathological changes associated with intestinal damage and the inevitable processes that occur during acute poisoning in other abdominal organs (and not only) makes recommendations for the treatment of such diseases rather uncertain [60].

Changes in the intestinal microbial landscape as a result of exposure to cyanobacterial metabolites are confidently named among the factors that contribute to the development of digestive tract pathology [52, 59]. Migration of microorganisms usually occurs from the distal intestine to its proximal fragments and into the stomach. At the same time, some members of the microbiota die, while for others, on the contrary, conditions are created for intensive reproduction. Several reasons are suggested leading to changes in the microbiota. Among them are the antimicrobial properties of the toxins themselves, the production of antimicrobial compounds by cyanobacteria, suppression of intestinal immunity, and destruction of the intestinal wall with limitation of its barrier function [48, 58].

The production of antimicrobial compounds by cyanobacteria is well studied [61]. It is considered not only a factor that can negatively affect the intestinal microbiota but also a potential opportunity to obtain new antimicrobial drugs. Dozens of compounds with antimicrobial properties have been found that are produced by cyanobacteria. Producers include members of the toxin-producing genera *Microcystis, Dolichospermum* (better known under the now obsolete but often used name *Anabaena*), *Lyngbya, Nostoc, and Nodularia* [7]. Antimicrobial compounds produced by cyanobacteria belong to various chemical groups: peptides, alkaloids, nucleosides, etc. Some of them have a structure similar to that of well-known antimicrobial drugs (macrolides, ketolides, benzoic acid, cyclic peptides, etc.). The spectrum of their antimicrobial action is multivariate. Some have antibacterial and antifungal activity, others anti-

protozoal and antiviral activity. Compounds that suppress the immune system and inhibit carcinogenesis are known.

Carcinogenicity of cyanotoxins

Among the most controversial problems associated with cyanobacteria is their carcinogenicity. Some authors are convinced that chronic intoxication leads to malignant degeneration of human tissues [62, 63], while others consider this assumption not yet proven [16, 64]. Opponents of carcinogenesis caused by cyanotoxins admit that they can stimulate malignant growth if the tumour already exists.

Among the cyanotoxins capable of causing the malignant transformation, microcystins, nodularins, and cylindrospermopsins are mentioned most frequently [62, 65]. However, it is obvious that the most studied cyanotoxins have been named. The carcinogenicity of other toxic metabolites has not yet been studied enough. Moreover, clinical observations suggesting the existence of a relationship between cyanotoxins and cancer only concern microcystins. The carcinogenicity of other toxins is based on experimental data.

The opinion on the ability of cyanotoxins to cause cancer is based on their genotoxicity [64]. It was demonstrated in an experiment on the expression of oncogenesis with repeated long-term administration of microcystins to animals. The ability of microcystins to suppress the activity of protein phosphatases leading to the formation of abnormal cells is particularly emphasised [62, 64].

Speaking of malignant neoplasms in humans caused by cyanotoxins, they usually refer to cancer of the large intestine, rectum, and liver. Long-term consumption of water and products containing trace amounts of cyanotoxins (usually microcystins) is believed to lead to the appearance of tumours of precisely this localisation [16, 64]. In 2010, microcystin was listed as an oncogene by the International Agency for Research on Cancer (IARC) [51].

In addition to microcystins, supporters of the carcinogenicity of cyanotoxins include other metabolites of cyanobacteria, primarily nodularins and, with reservations, cylindrospermopsin, among cancer-causing agents [16, 62]. Convincing results of clinical observations have not yet been provided. However, experimental data suggest such a possibility. In addition to suppressing the activity of protein phosphatases and inducing the formation of aggressive oxygen radicals, cyanotoxins are able to suppress the activity of the cellular suppressor of tumour degeneration and, at the same time, activate genes that promote the malignant transformation of cells. Animal studies, while limited, generally allow for the possibility of oncogenesis induction by cyanotoxins. However, all researchers agree that this issue has not been studied enough and deserves more attention.

Conclusions

Toxic metabolites produced by cyanobacteria pose a real threat to human and animal health and life. Cyanotoxins can cause severe damage to the central and peripheral nervous systems, liver, kidneys, reproductive system, digestive tract, etc. There is reason to talk about the immunosuppressive effect of these toxins. Several studies suggest the possibility of the influence of cyanobacterial metabolites on carcinogenesis, especially in the liver, colon, and rectum. There is a discussion about the role of cyanotoxins in severe degenerative processes in the human brain. Numerous cases of mass death of domestic, agricultural, and wild animals that have used products (usually water) containing cyanotoxins are well known.

Humans and animals may come into contact with toxic metabolites of cyanobacteria in a variety of ways. For credible reasons, their number will grow including such contacts that are not obvious. Today, the possibility of the criminal use of cyanotoxins cannot be ruled out.

All this indicates the need to study cyanobacteria, their role in the etiology of human and animal diseases, and the pathogenesis of cyanotoxin poisoning. It is necessary to pay serious attention to the clinical manifestations of the pathological processes caused by cyanotoxins, the development of diagnostic methods, and specific therapy for poisoning.

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Author contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published.

The article was submitted 13.01.2022;
accepted for publication 14.03.2022;
published 29.04.2022

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Участие авторов. Все авторы внесли существенный вклад в проведение поисково-аналитической работы и подготовку статьи, прочли и одобрили финальную версию до публикации.

Статья поступила в редакцию 13.01.2022;
принята к публикации 14.03.2022;
опубликована 29.04.2022