Journal of Experimental and Basic Medical Sciences 2022;3(2):103-108

Review

Human Health Impact of Cyanobacterial Toxins

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ABSTRACT

Cyanobacteria are prokaryotic organisms that differ from other eukaryotic algae by the absence of membranous organelles and plastids. Being primary producers, they have very important duties in the biosphere. Being phototrophs, they have a high amount of oxygen production in the biosphere. In addition to its positive aspects, cyanobacteria produce various toxins against environmental influences. The increase of these toxins in fresh waters and seas poses a great threat to humans, animals and plants. The diversity of toxins develops in direct proportion to their mechanism of action. Cyanotoxins, which have negative effects on human health, are specific with their hepatotoxic, neurotoxic, genotoxic, cytotoxic and effects. Toxic cases that can lead to death may occur if the necessary interventions are not made in the poisonings that may occur due to the exposure of people to cyanotoxins. In this review, the toxic effects of cyanotoxins on human health were discussed according to their mechanism of action.

Keywords: Cyanobacteria, cyanotoxin, cytotoxicity, genotoxicity, hepatotoxicity, neurotoxicity

Cyanobacteria, which serve as the primary producers of oxygen in nature, have played important key roles in Earth's evolutionary history.[1] They are the only prokaryotic organisms that provide oxygenic photosynthesis. For this reason, it is responsible for the increase in the amount of oxygen in the ocean and atmosphere during the great oxidation event, aided by geological processes.[2,3] Cyanobacteria, like other organisms, have a cytoplasmic membrane and an outer membrane rich in peptidoglycan as Gram-negative eubacteria.[4]

Cyanobacteria have various biological and biochemical activities. These activities allow them to form secondary metabolites called cyanotoxins.[5] It is known that approximately 60% of cyanobacteria samples examined globally contain toxins.[6] The overgrowth of cyanobacteria and the increase in their amount in water is called "bloom".[7,8] These blooms can cause the poisoning of many animals in nature.[9] People can be exposed to cyanotoxins by ingesting contaminated water and food sources, coming into contact with contaminated water sources, and inhaling aerosolized toxins.[10] Cyanotoxins are classified as cyclic peptides, alkaloids, and lipopolysaccharides according to their chemical structure. In addition, according to their mechanism of action, cyanotoxins are classified as hepatotoxins, cytotoxins, and neurotoxins.[11,12]

Research in terms of monitoring, properties, production, and analysis of certain cyanotoxins and cyanobacteria with toxigenic properties has increased considerably in recent years.[13,14] In this review, the types, modes of action, and negative effects of cyanobacteria toxins on human health were discussed.

CYANOBACTERIAL TOXINS

There are many metabolites directly responsible for the reproduction, development, and growth of cyanobacteria. Apart from these, there are also various toxin metabolites that aim to increase survival against other organisms at a high rate.[15] These toxins have significant harmful effects on other cells, tissues,

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Cite this article as: Soydan S, Erbaş O. Human Health Impact of Cyanobacterial Toxins. JEB Med Sci 2022;3(2):103-108.

doi: 10.5606/jebms.2022.1016

Received : June 15, 2022
Accepted : June 26, 2022
Published online : September 12, 2022

or organisms.[16]

It is very important to determine whether cyanobacteria have the ability to produce toxins. For the accurate identification of toxin-producing cyanobacteria, visual identification and molecular analysis of a good taxonomist in the field is required. Quantitative cyanotoxins analysis should be performed for conclusive conclusions that the toxin was actually produced.[17–19]

Data from environmental poisoning cases and bioassays of biomass of cyanobacteria revealed signs of the presence of specific cyanobacteria before purification and structural characterization of cyanotoxins.[20] Also, even toxic strains do not automatically produce toxins. Many cyanobacteria reach the ability to produce toxins by turning certain specific genes on and off under the influence of environmental conditions. Thus, identifying crimes involving these specific genes is an important way to determine whether a bloom is toxic.[21]

Most cases of toxic poisoning occur due to thick layers of deposits on the water surface. People generally avoid direct contact with the high concentration of cells thus formed. Therefore, acute poisonings are not very common.[22] Health data obtained in humans and animals exposed to the toxic effects of cyanobacteria vary according to the types of cyanotoxins.[23] Cyanotoxins are grouped as cytotoxins, hepatotoxins, and neurotoxins according to the affected cells, tissues, organs, and physiological systems.[24] For example, hepatotoxins include nodularin (NOD), microcystin (MC), and cylindrospermopsin (CYN). However, it also has neurotoxic and hepatotoxic properties. As another example, saxitoxins (STXs) and anatoxins are neurotoxins produced by some species of cyanobacteria.[25]

NEUROTOXIC EFFECTS OF CYANOTOXINS

The toxins produced by some cyanobacteria are included in the neurotoxins included in the class of additional compounds due to the neurological connections they affect. In this context, it has been found that cyanobacterial compounds with toxic properties, which are not generally accepted as neurotoxins, may also have neurological effects or enter the central nervous system (CNS).[26]

The ability of cyanobacterial neurotoxins to cross the blood-brain barrier is the most important specific feature that allows them to easily enter the CNS.[27]

Some of the cyanobacterial neurotoxins include anatoxins. Among them, anatoxin-a, which is an alkaloid, and its other derivatives are structurally similar to cocaine. Anatoxins are highly potent neurotoxins produced by genera of cyanobacteria such as Oscillatoria, Microcystis, Anabaena, Nostoc, Cylindrospermum, Aphanizomenon, Arthrospira, and Phormidium. Although anatoxins are not among the most common toxins in the world, they pose serious health risks to aquatic and terrestrial creatures and even cause death due to their high toxicity values.[28] There are two anatoxin-a variants. These are anatoxin-a and homoanatoxin-a.[29] They bind to nicotinic receptors. Anatoxin-a is a specific alkaloid with a low molecular weight. Semi-hard bicyclic is in the secondary amine group. This bicyclic structure of anatoxin-a and the ketone group of the specific conjugated type significantly restrict its conformation.[30–33] The reason acetylcholine esterases cannot remove these neurotoxins from the main CNS receptor is that the anatoxins work as a kind of mimic of acetylcholine. This event results in the successive stimulation of neurons and their subsequent depolarization. These properties make them powerful agonists. In addition, the mechanism of action of anatoxins is quite rapid.[34,35] Symptoms such as a decrease in locomotor activity, rapid loss of coordination, irregular breathing, change in gait, paralysis of the peripheral skeletal and respiratory muscles, tremors, and, even worse, contractions that appear before acute death are examples of the acute effects of anatoxins in vertebrates.[36]

The toxic properties of cyanobacteria detected in freshwater and marine environments are widely known. In addition, it was determined that terrestrial-type cyanobacteria found in caves in limestone and soil structures also contain toxins. The most common example of this toxin is β-N-methylamino-l-alanine (BMAA).[37]

Cyanobacteria, such as the symbiotic *Nostoc* spp. found in desert crusts, are another example of BMAA-containing species. The BMAA is not only of cyanobacterial origin. In recent studies, it has been found that it is also found in phytoplankton.[38] Blooms of cyanobacteria in water or ingestion of aquatic organisms exposed to these blooms are sufficient for humans to be affected by BMAA toxin.[39]

Oxidative stress causes cellular death together with mitochondrial dysfunction in neurodegenerative diseases.[40-43] BMMA is known to cause mitochondrial damage. It has a specific effect on the pro-inflammatory profile in neurodegenerative diseases.[44]

In recent years, toxicological studies have shown that BMMA can be incorporated into the protein structures of nerve cells incorrectly and cause protein misfolding, neuron damage, and oxidative stress. Accordingly, BMMA toxin is being examined in many studies, taking into account the correctness and validity of the hypothesis of misfolding in proteins, the main mechanism of toxicity and ecotoxicity in recent years, and also the possibility of inhibition of certain specific enzymes that directly interfere with the folding of proteins.[45]

HEPATOTOXIC EFFECTS OF CYANOTOXINS

The specificity of hepatotoxins can be studied *in vitro* or *in vivo*. *In vivo* studies provide the privilege of preserving the structural integrity, biochemical and natural physiological environment of the liver.[46,47] Thus, data can be obtained better. Therefore, a large number of experimental animals will be required for the processes that are frequently performed in relation to hepatotoxicity tests. This process is limited by ethical considerations as well as economic constraints.[48]

The vast majority of hepatotoxins can be generally referred to as microcystin. The reason is that the first hepatotoxin discovered was isolated from *Microcystis aeruginosa*. Approximately 50 different microcystin toxins have been isolated. Some of these toxins can be easily produced by *Microcystis aeruginosa* during the formation of a bloom.[49]

Microcystins resist gastrointestinal-mediated digestion. It is then concentrated in the liver with an active transport system. In acute poisoning, hemorrhagic shock occurs with liver damage and blood loss.[50]

When viewed for progression, microcystins and another hepatotoxin, nodularin, enter the bloodstream after consumption. Consumption takes place with the ileum. They are then transferred to hepatocytes through the transport system developed with bile acid salts. Hepatotoxins cause deterioration in the structure and consistency of endothelial cells in the capillaries of the portal circulation, damage to the cellular skeleton with various changes in actin microfilament structures, blood loss, intrahepatic hemorrhage, and liver failure.[51] They also inhibit protein phosphatase type 1 or type 2A (PP1 or PP2A), which is involved in the basic control of cellular structure and function in liver cells.[52]

GENOTOXIC AND CYTOTOXIC EFFECTS OF CYANOTOXINS

The main mechanism of toxicity in cyanotoxins has been found to be irreversible inhibition, which developed due to protein synthesis.[53] In this context, the processes of inducing genotoxicity effects are still not fully understood. In many test systems, the toxin is reported to be genotoxic and carcinogenic. It also causes significant deoxyribonucleic acid (DNA) damage. There is considerable evidence of the need for metabolic activation of cytochrome p450 enzymes to be implemented in the studies of genomic indecision.[54]

Cyanobacterial toxin cylindrospermopsin (CYN) produced by *Cylindrospermopsis raciborskii* is the primary target of the liver. However, it was also described as a cytotoxin due to adverse effects on many organs.[55] The CYN is also involved in the literature as a pro-genotoxic. So it's reported that metabolic activation is necessary for it to show its effects cytotoxic and/or genotoxic.[56] Two mechanisms have been established for the detection of genetic activity: i) loss of kinetochore/spindle functions; ii) induction of DNA strand breaks (SBs) at the DNA level.[57] Genotoxicity-based properties of these identified mechanisms are still being investigated.[55]

When an experiment is designed, DNA breaks can be detected by comet assay in murine hepatocytes. However, it cannot be detected in the Chinese hamster ovary (CHO K1) cells. This states that metabolic activation is necessary for the genetic effect to occur. In addition, researchers have reported in several studies that CYN toxicity mediates cytochrome p450 (CYP) metabolites.[58]

It is very important to elucidate the mechanisms that lead to cyanotoxin-induced carcinogenesis. Researchers have shown that cyanotoxins prevent chromatin condensation and prevent the formation of metaphase chromosomes, affecting the chromatin-specific structure. Apart from influencing chromatin-specific structural modifications, chemically induced carcinogenesis produces a spiral in abnormal structure. This suggests that CYN may be linked to a possible carcinogenic effect.[59]

In conclusion, the effect of cyanobacterial toxins at the cellular level comes to the forefront with serious damage. In neurological damage, stress conditions, neuron damage, and agonist characters are prominent. In hepatotoxic and cytotoxic influences, the inhibition of protein phosphatases and cellular

structure disorders occur frequently. The direct relationship of genotoxic effects to cytotoxicity leads to chromatin abnormalities and DNA-level damages. Therefore, the harms of cyanobacterial blooms that may occur as a result of the destabilization of the ecosystem in water resources to human, animal, and plant health should not be ignored with their specific effects.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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