Review paper

Dermatotoxins synthesized by blue-green algae (*Cyanobacteria*)

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Abstract

In this paper we have reviewed dermatotoxins produced by blue-green algae. Dermatotoxins are harmful compounds that target human skin. Blue-green algae (*Cyanobacteria*) are prokaryotic microorganisms, mainly found in the water environment – marine and freshwater. A number of species are able to synthesize several toxic substances that affect human health upon exposure to lyngbya-, aplysia- and debromoaplysiatoxin. Lipopolysaccharides present in cyanobacteria cell walls can be irritating to human skin. Therefore, surface waters for recreational use should be monitored for the presence of toxic species of blue-green algae.

Key words: blue-green algae, cyanotoxins, dermatotoxins, lyngbyatoxin, aplysiatoxin, debromoaplysiatoxin.

Introduction

Blue-green algae (*Cyanobacteria*) are a group of prokaryotic, autotrophic microorganisms that contain the photosynthetic pigments (chlorophyll and phycocyanin). So far over 2,500 species have been identified, mainly related to ecosystems of surface waters, both marine and freshwater [1, 2]. Almost 80 species were recognized as able to synthesize toxic metabolites showing activity especially against the warm-blooded vertebrates [3, 4]. These chemical compounds include alkaloids, cyclic peptides and lipopolysaccharides with a wide spectrum of health effects: hepatotoxic, neurotoxic, cytotoxic as well as dermatotoxic [5]. Cyanotoxins are released mainly during the rapid growth phase called blue-green algae blooms. This phenomenon is based on the mass reproduction of a particular type of *Cyanobacteria* species for a period of several days and is manifested by the appearance of blue-green color of water and foam, scum, or mats floating on the water surface. In the temperate climate, blooms are formed during high availability of nutrients (mineral nitrogen and phosphorus), elevated temperature and limited water waving. The problem of the direct exposure to cyanotoxins exists primarily in the summer and early autumn [6, 7]. Because of the tendency of these compounds to accumulate in the invertebrate tissues (shrimps, clams, snails) and fish, there is a risk of health complications as a result of consumption of food of unknown origin [5, 8, 9]. A new Regulation of the Minister of Health dated 8 April 2011 on the supervision over the quality of bathing water and the areas used for swimming provides for, among others, the necessity of monitoring of water used for recreation for dangerous algal blooms [10].

This study aims to characterize the dermatotoxic group of chemical compounds produced by *Cyanobacteria* and to determine their potential impact on human health.

Lyngbyatoxins

Lyngbyatoxins (LA) are indole alkaloids, their name was taken from a cyanobacteria genus *Lyngbya* (order: *Oscillatoria*) [11]. The main producers are filamentous cyanobacteria: marine *L. majuscule* and freshwater *L. wollei* – both able to form significant colonies that reveal as green mats floating on the water surface. Three isoforms of lyngbyatoxin were identified: a, b and c; their molecular mass is 437 Da [12, 13]. The structure of lyngbyatoxin-a is identical to an isomer of teleocidin A, isolated from mycelium of several species of *Streptomyces* [14]. LD_{50} for mice (oral route) is 250 µg/kg [15].

Massive occurrence of *Lyngbya majuscula* was found in almost 100 locations around the world including trop-

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ical, subtropical as well as temperate zones [12]. So far *L. majuscula* has not been identified on the Polish coast of the Baltic Sea. However, there is a risk of expansion in this area, due to the confirmed presence in the region of Kattegat Strait, Cape Arkona and the Gulf of Riga [16].

Lyngbyatoxin-a has a skin tumour promoting activity similar to 12-O-tetradecanoylphorbol-13-acetate (TPA) basing on the activation of protein kinase C (PKC) as a result of replacing endogenous activator of this enzyme – 1,2 diacyloglycerol. The observed damages of nexus junctions are most likely induced by connexin phosphorylation of PKC [17, 18]. Lyngbyatoxin-b and lyngbyatoxin-c have 1/200th and 1/20th the activity of lyngbyatoxin-a, respectively [12]. Lyngbyatoxins are slightly lipophilic, penetration through human skin after 1 h of exposure to 26 μg/cm^2 was estimated as 6% of the dose [19].

Medical literature described several confirmed cases of significant lyngbyatoxins effects on humans having contact with water resources with high occurrence of *Lyngbya*. The most common symptoms involve skin and are usually defined as "seaweed dermatitis" [20]. Osbourne *et al.* examined a group of 5000 marine recreational users in northern Moreton Bay (Queensland, Australia) during a period of *L. majuscula* occurrence. The most frequently observed symptoms were: skin itching (23%), skin redness (10.5%), skin burning (10.5%), skin blistering (2.2%) and skin swelling (0.8%) [21]. These symptoms were most intense in genital, perineum and perianal areas [12, 22]. The irritant properties of lyngbyatoxin also affected ears (sore, discharge) and eyes (sore). The most frequent general symptoms were headache, nausea, vomiting and diarrhea probably resulting from simultaneous ingestion of intact cyanobacterium with water [23]. Young adults (18-29 years of age) had the highest sensitivity to lyngbyatoxin. First symptoms occurred within a few minutes to a few hours after exposure. Visible dermatitis with redness began to occur after 3-20 h and lasted for 2-12 days. No connection between the type of symptoms and their intensity with duration of bathing was found. Similar symptoms were observed for people staying in water from 2 min to 4 h [24, 25].

Histopathologic examination of human skin exposed to *L. majuscule* (topical application) found acute, vesicular dermatitis. Superficial desquamation and edema of the epidermis was apparent in the microscope image. Within the epidermis (stratum malpighii) numerous vesicles of various size were observed. Some vesicles contained red blood cells and polymorphonuclear leukocytes which were also present in the deepest part of epidermis. The superficial dermis showed the infiltration of chronic and acute inflammatory cells including mononuclear cells, eosinophils and neutrophils [24].

Lyngbyatoxins can also be carried by wind in an aerosolized form and cause a health risk for people not exposed to water. *L. majuscula* dermatitis was diagnosed in subjects walking on the beach during strong winds. Most common symptoms included facial rash, groin and torso skin itching, conjunctivitis, inflamed eyes and lacrimation [26, 27]. Fishers cleaning fish nets and crab pots from *L. majuscula* also reported skin and eye irritation [28].

Osbourne *et al.* [27] listed treatment methods for *Lyngbya*-induced dermatitis that included: ice packs, loratadine (10 mg/day) and 1% hydrocortisone cream (topically four times daily).

Another issue associated with *Cyanobacteria* able to synthesize lyngbyatoxins is their accumulation in tissues of aquatic organisms being a source of food as sea turtles *Chelonia mydas* [29]. Consumption of such products, as well as ingestion of water containing lyngbyatoxin leads to inflammation of the esophagus and digestive tract [17].

Aplysiatoxin and debromoaplysiatoxin

Aplysiatoxin (AT) and debromoaplysiatoxin (DAT) belong to phenolic bislactones. Their molecular mass is 671 Da and 592 Da, respectively [30]. They were first isolated from marine mollusks belonging to *Stylocheilus* genus [31], feeding upon *Cyanobacteria* species from *Lyngbya*, *Schizothrix* and *Planktothrix* genus that have an ability of AT and DAT synthesis [17]. Chemically the only difference between aplysiatoxin and debromoaplysiatoxin is that the phenolic structure of AT is replaced with single bromine atom in DAT [32].

Several experimental studies showed the potential negative impact of aplysiatoxin and debromoaplysiatoxin on mammals' health. In mice, both toxins caused severe ear irritation [33]. Inhibition of epidermal growth factor (EGF) (10 times higher for aplysiatoxin) [34] and activation of ornithine decarboxylase in human skin cells was observed [35]. Both substances are considered to have tumorigenic properties and are activators of protein kinase C [36]. Aplysiatoxin and debromoaplysiatoxin caused differentiation of HL-60 cells into macrophages [37]. Applied topically, debromoaplysiatoxin was found to cause an irritant pustular folliculitis in humans and severe cutaneous inflammatory reaction in the rabbits and in hairless mice [25]. Direct contact with aplysia- and debromoaplysiatoxin contaminated water caused acute skin irritation, rashes and blisters [12, 38, 39]. There is also a risk of inhalation of aplysia- and debromoaplysiatoxin from aerosols transported by the wind along the coasts. Willey *et al.* [40] suggested that both toxins induce terminal squamous differentiation in normal human bronchial epithelial cells.

Bioaccumulation in aquatic organisms and potential biomagnification of AT and DAT are still poorly understood [41]. However, the tendency of some benthic snails to accumulate these toxins in different parts of the body was demonstrated [42]. Further analyses are necessary to esti-

mate the exposure possibility to AT and DAT by consumption of organisms obtained from water.

Lipopolysaccharides

Lipopolysaccharide (LPS) is commonly present in cyanobacterium cell wall, forming complexes with proteins and phospholipids. Its structure is made of lipid A, R-type core oligosaccharide and O-specific polysaccharide chains [43]. Toxicity of cyanobacterium LPS is lower than LPS of *Enterobacteriaceae*, although it differs between species. Orally, LD_{50} for mice varies from 40 mg/kg to 425 mg/kg. In most common blue-green algae *Microcystis aeruginosa* LD_{50} was 50 mg/kg [32, 44]. There are only few publications on impact of cyanobacterium LPS on human health and its mechanism of action remains unclear [33]. This is due to the difficulties in distinguishing the symptoms caused only by LPS and caused by secondary metabolites synthesized by blue-green algae. Therefore, the whole range of symptoms were attributed to LPS such as: skin [45, 46] and eye [47, 48] irritation, hay fever [49], respiratory problems [50], headaches and dizziness [51], blistering of mucous membranes and fever [52]. It must be assumed that contact with any water characterized by high concentration of *Cyanobacteria* can lead to human health complication, including dermatitis.

Conclusions

The role of dermatotoxic metabolites synthesized by blue-green algae in human health is still not clear. A few papers on this subject have been published due to dermatologic complications not being connected with cyanobacterium occurrence and production of a wide range of toxic compounds. Therefore, knowledge of the above substances is based mainly on studies of animal models. Described cases clearly reveal negative impact of lyngbya-, aplysia- and debromoaplysiatoxin on human skin, even during a short-term exposure. Health hazard concerns also people not directly using water resources but residing or walking near the coasts, especially in windy weather. Cyanobacterium toxins can be spread with aerosols from water surface causing dermatitis and allergic reactions. Prolonged exposure can lead to promotion of carcinogenesis. In the case of massive occurrence of blue-green algae (even species not producing toxic metabolites) there is a risk of exposure to lipopolysaccharide which in a few reports seems to have an irritant effect on human skin.

Climate change and water pollution can have a significant role in expansion of toxic *Cyanobacteria* [53, 54]. New locations of dermatotoxic species may occur and raise human health concern. Water resources used recreationally should be regularly monitored. Dermatologists should consider diagnosis of water-linked dermatitis for exposed patients.

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