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Neurotoxins From Marine Dinoflagellates And Diatoms: Source, Structure and Toxic Effects

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Abstract:

In recent decades, the occurrence and distribution of harmful algal blooms (HABs) have escalated, resulting in significant economic and public health challenges globally. Certain HAB species produce potent toxins that can contaminate shellfish and marine fish, leading to various seafood poisoning syndromes, including Paralytic Shellfish Poisoning (PSP), Neurotoxic Shellfish Poisoning (NSP), and Ciguatera Fish Poisoning (CFP). The principal culprits diatoms and dinoflagellates produce toxins like saxitoxin, brevetoxins, azaspiracid, and domoic acid, which impact human health through neurological and gastrointestinal symptoms. Specific toxins, such as palytoxins and yessotoxins, reveal complex mechanisms of action, targeting ion channels in neurons. The widespread and increasing toxicity across marine ecosystems poses risks not only to human consumers but also to sea mammals and birds. With the urgency of rapid diagnosis and treatment, as well as prevention measures for algal blooms, understanding these neurotoxins is crucial for future health strategies and potential therapeutic applications.

Keywords: Paralytic shellfish poisoning (PSP), Domoic acid, Algal blooms, ciguatera fish poisoning (CFP), amnesic shellfish poisoning (ASP), neurotoxic shellfish poisoning (NSP), azaspiracid toxins, yessotoxin, palytoxin

Introduction:

In many parts of the world, the frequency and geographic spread of harmful algal blooms (HABs) have grown throughout the last few decades. This has caused negative effects on the economy and public health, and it is now a global issue. Certain HAB species are known to create strong toxins that can affect human health when consumed by contaminated shellfish, coral reef fish, and finfish, or when exposed to water or aerosols. Toxic species are frequently found in trace amounts with no negative effects on the

environment or human health. However, poisons build up in filter-feeding shellfish, zooplankton, and herbivorous fishes and are transported to higher trophic levels. Diatoms and dinoflagellates, a very broad and varied category of eukaryotic algae in the marine environment, are the main producers of toxins that affect people among those causative organisms. The toxicology and pharmacology of diatoms and dinoflagellate toxins have been the subject of extensive research in recent decades. Five major seafood poisoning syndromes caused by toxins have been identified from these species: ciguatera fish poisoning (CFP), amnesic shellfish poisoning (ASP), diarrheic shellfish poisoning (DSP), neurotoxic shellfish poisoning (NSP) and paralytic shellfish poisoning (PSP). Several new poisoning symptoms caused by recently discovered dinoflagellate toxins, like azaspiracid toxins, yessotoxin and palytoxin, have been found and described recently in addition to these well-known poisonings.

Structure, Mechanism of Action and Toxicity syndromes:

Paralytic Shellfish Poisoning (PSP):

Consuming shellfish contaminated with toxic dinoflagellates can result in PSP, a global marine toxin illness that causes both neurological and gastrointestinal symptoms. A. catenella, a dinoflagellate, was responsible for the first PSP occurrence, which was documented in 1927 close to San Francisco, USA, and left 102 people sick and six dead. Since then, it has been found that the main sources of PSP toxins are members of three dinoflagellate genera: *Pyrodinium, Alexandrium and Gymnodinium*. PSP poisons are non-proteinaceous toxins that are water soluble and heat stable. Of the toxins linked to PSP, saxitoxin is the most hazardous and the one that has been investigated the most. Its oral LD50 in mice is 263 µg/kg body weight, while its peritoneal LD50 is 3–10 µg/kg body weight. One to four milligrams is the lethal oral dose for humans. PSP symptoms include numbness in the extremities, breathing difficulties, gastrointestinal issues, a tickling sensation in the lips, mouth, and tongue, and a feeling of dissociation that is followed by total paralysis. The most well-known strong neurotoxins that selectively and precisely bind to excitable cells' sodium channels are PSP toxins. By inhibiting the muscular action potential without depolarizing cells, saxitoxin also directly impacts skeletal muscle, eliminating peripheral nerve transmission.

Neurotoxic Shellfish Poisoning (NSP):

When shellfish exposed to blooms of the dinoflagellate *Kerenia brevis* (previously Gymnodinium breve) are consumed, NSP results. The two lipid-soluble poisons produced by this dinoflagellate species are haemolytic and neurotoxic, and they kill large numbers of fish, birds, and marine mammals. Brevetoxins, a group of ladder-like polycyclic ether toxins, are the neurotoxic toxins. Brevetoxin B (type 1; PbTx-2, 3, 5, 6, 8, 9) and brevetoxin A (type 2; PbTx-1, 7, 10) are the two types of brevetoxin congeners based on their backbone structure. Among them, PbTx-2T is the major brevetoxin produced by *K. brevis*. Brevetoxins are acid and heat stable (they may withstand

temperatures of up to 300°C), tasteless, and odourless. The mouse LD50 is 520 µg/kg body weight taken orally, 94 µg/kg body weight given intravenously, and 170 µg/kg body weight (0.15–0.27) given intraperitoneally. Compared to PSP, NSP manifests as a milder gastroenteritis with neurologic symptoms. Nausea, perioral tingling and numbness, loss of motor function, and excruciating muscle pain are all signs of NSP. Brevetoxins are thought to be depolarizing chemicals that open voltage-gated sodium ion channels in cell walls, causing an uncontrollable Na+ influx into the cell. Their mode of action has been thoroughly investigated. Research using rat synaptosomes and neuroblastoma cells has demonstrated that brevetoxins have a 1:1 stoichiometry of action on neurotoxin binding site 5 on the α-subunit of the voltage-dependent sodium channel. PSP toxins work differently because they block the sodium channel, which stops sodium ions from getting through nerve cell membranes.

Ciguatera Fish Poisoning (CFP):

Consumption of poisoned coral reef fish, including barracuda and snapper, is the cause of CFP, the most often reported marine toxin disease worldwide. Ciguatoxins are thought to affect about 25,000 individuals a year, and CFP is considered a global health issue. It has been determined that the dinoflagellate species *Gambierdiscus toxicus* is the source of ciguatera toxins. This species initially creates maitotoxins (MTXs), which are the lipophilic precursors of ciguatoxin. Herbivorous fishes and invertebrates that feed on G. toxicus biotransform these precursors into ciguatoxins, which are then accumulated at higher trophic levels. The family of heat-stable, lipid-soluble, highly oxygenated, cyclic polyether compounds known as ciguatoxins shares structural similarities with brevetoxins. It is important to note that the symptoms of ciguatera differ depending on the ocean: in the Pacific, neurological symptoms are more common, but in the Caribbean, gastrointestinal symptoms are more common because of the distinct toxin makeup. Ciguatoxins work similarly to brevetoxins, which specifically target the α-subunit of neuronal sodium channels' common binding site 5. However, CTX-1 has an affinity for voltage-dependent sodium channels that is about 30 times greater than that of brevetoxin because ciguatoxins have a higher affinity than brevetoxins. Ciguatoxins cause cell depolarization, an influx of Na+ ions, and the emergence of spontaneous action potentials in excitable cells by opening sodium channels throughout the peripheral nerves, especially at the nodes of Ranvier.

Azaspiracid Shellfish Poisoning (AZP):

Initially discovered in the Netherlands, azaspiracid poisoning (AZP) has since spread throughout Europe. It is brought on by eating contaminated shellfish linked to the dinoflagellate *Protoperidinium crassipes*, which could produce large intracellular quantities of the lipophilic polyether toxin azaspiracid (AZA1). AZP is characterized by severe diarrhoea, cramping in the

stomach, nausea, and vomiting. Additionally, neurotoxic effects were noted. It has been postulated that it binds to Ca channels for which neurological signs are seen.

Yesserotoxins (YTX):

The scallop *Patinopecten yessoensis* is the original source of YTX and its equivalents, which are disulphated polyether chemicals that are becoming more and more common in seafood. *Protoceratium reticulatum, Lingulodinium polyedrum* and *Gonyaulax spinifera* are additional species that produce these poisons. For neurons, YTX is a strong neurotoxic. Nevertheless, neither the mechanism nor the site of action is known. In cerebellar neurons, YTX was found to cause a two-fold rise in cytosolic calcium, which was stopped by the voltage-sensitive calcium channel antagonists verapamil and nifedipine. These findings imply that YTX may directly interact with sodium and/or calcium channels. According to a histopathological analysis, YTX caused changes in the Purkinje cells of the cerebellum such as cytological harm to the cell body of the neuron and modifications to the immunoreactivity of the neurotubule and neurofilament.

Palytoxins (PTX):

PTX is a polyhydroxylated molecule, exhibits significant biological activity at low concentrations. *Palythoa toxica*, a soft coral, was the first to isolate this toxin, which then spread to seaweeds and shellfish. Palytoxin was recently discovered in *Ostrepsis siamensis* is a benthic dinoflagellate. PTX is a complex molecule with lipophilic and hydrophilic sections, boasting the longest chain of continuous carbon atoms in any natural substance. PTX is a highly powerful toxin, with LD50s ranging from 0.025 µg/kg in rabbits and dogs to 0.45 µg/kg in mice, and 0.9 µg/kg in monkeys, rats, and guinea pigs 24 hours after intravenous administration. Toxic symptoms include fever, inactivity, ataxia, sleepiness, and weakness of limbs, leading to death. PTX preferentially binds to the Na+, K+-ATPase, converting it into a channel permeable to monovalent cations with a single-channel conductance. PTXs are thought to have three basic sites of action: opening a modest conductance, non-selective cationic channel, causing membrane depolarization, K+ efflux and Na+ influx.

Domoic acid (DA)

Pseudo-nitzschia australis, a diatom, produces domoic acid during certain severe algal bloom episodes. This neurotoxic accumulates in small fishes like sardines and anchovies, which are then consumed in high quantities by marine mammals such as sea lions. Domoic acid affects the brain and heart, resulting in seizures and heart failure. If left untreated, it typically results in permanent brain damage. The toxin will eventually leave an animal's system, but sea lions who are repeatedly exposed to it will suffer longer and more devastating consequences. Southern sea otters have also been impacted by DA toxicity. Lesser scaup, Brandt's cormorants, and

brown pelicans are among the sea birds that have succumbed to DA toxicosis. Domoic acid's actions have been attributed to a variety of processes, the most concerning of which involves glutamate receptors. Domoic acid is an excitatory amino acid derivative of glutamate, which acts as a neurotransmitter in the brain by activating glutamate receptors. Domoic acid has a high affinity for these receptors, resulting in excitotoxicity caused by an integrative action on ionotropic glutamate receptors on both sides of the synapse, together with the effect of blocking the channel from rapid desensitization. Furthermore, endogenous glutamate and N-Methyl-D-aspartate receptor agonists have a synergistic impact, contributing to excitotoxicity. Domoic acid specifically damages the amygdaloid nucleus and the hippocampus in the brain. By triggering kainate and AMPA receptors, which results in a calcium influx, it harms the neurons. Despite the fact that calcium entering cells is natural, unchecked calcium buildup leads to cell degeneration. The hippocampus may sustain significant injury, which results in short-term memory loss.

Conclusions:

The neurotoxins produced by diatoms and dinoflagellates are having potential impacts on health of human, animals and birds. These are consumed by fishes and other marine creatures which in turn affects other higher vertebrates upon consumption. All these toxins are not fully characterized but some of them are well studied in terms of pharmacological actions, receptor binding and molecular structure. In future this can be exploited to treat diseases. As these affect many humans and animals in small time rapid diagnosis and treatment is necessary. Prevention of algal bloom is important to reduce toxin production.

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