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Editorial Open Access

Marine Algal Toxins: Seafood Safety, Human Health and Beyond

Olga M Pulido*

Adjunct Professor, Department of Pathology and Laboratory Medicine, University of Ottawa, Ottawa, ON, Canada

***Corresponding author:** Olga M Pulido, Adjunct Professor, Department of Pathology and Laboratory Medicine, University of Ottawa, Ottawa, ON, Canada, E-mail: opulido@uottawa.ca

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Editorial

Food is an important potential route of oral exposure to environmental toxic agents worldwide. Factors such as agricultural and dietary practices, geographic regions and population characteristics including genetics, age, co-morbidities, and nutritional status may greatly influence the exposure level and host response/s to potential toxic agent. Regulatory systems are pivotal to maintain safe and nutritious sources of food supply. Key to health risk assessment is the identification of xenobiotic induced adverse effects, their source, and their mechanisms of action [1].

Seafood is a major internationally traded commodity that can be associated with food-borne illness, including intoxications, allergies and infections. Marine algal toxins are a major source of seafood contamination worldwide with serious adverse impacts to human health, wildlife, the economy, and the ecosystem. Unicellular algae under certain conditions can proliferate and aggregate to form dense concentrations of cells or "blooms", which may discolor the water red, brown or green giving rise to the term "red tide". Phytoplankton species such as dinoflagellates, diatoms and cyanobacteria that produce toxins are included under the general term "harmful algal blooms" (HABs), and their toxins under the term "Phycotoxins".

The conditions that trigger the occurrence of toxic phytoplankton species and/or production of toxins are not fully understood. Several environmental and climatic factors have been implicated in explaining the apparent increase in HABs worldwide. Toxins produced by cyanobacteria known as cyanotoxins, preferentially contaminate soft water, including drinking water [1,2]. Marine phytoplankton, primarily dinoflagellates and diatoms, produce toxins that preferentially contaminate seawater, described as "marine biotoxins". These toxins accumulate in seafood such as molluscan shellfish tissues and may pose a direct threat to consumers. Once contaminated, some shellfish depurate the toxins relatively quickly whereas others can retain them for months and even years, particularly in the digestive gland and the gonads. In humans, the health impact of algal toxins has been observed only under acute conditions; the effects of chronic exposure to low levels are poorly understood or documented. The health risks associated with emerging toxins have not been studied in detail. The principal clinical syndromes currently recognized to be caused by ingesting seafood contaminated with marine biotoxins from HABs are: amnesic shellfish poisoning (ASP), diarrheic shellfish poisoning (DSP), neurotoxic shellfish poisoning (NSP), paralytic shellfish poisoning (PSP) and ciguatera fish poisoning (CFP). Domoic acid, a potent algal toxin, is an example of the human and wildlife health impact of an algal toxin. It is also a prototype of the biomedical research development arising from the use of a marine biotoxin as investigational tool [3-5].

Domoic acid was first identified as a causative agent of shellfish poisoning in 1987, when scores of people in Canada were poisoned after consuming contaminated blue mussels (*Mytilus edulis*). The poisoning was characterized by a constellation of clinical symptoms and signs involving multiple organ systems: the gastrointestinal tract, the central nervous system (CNS) and the cardiovascular system. Among the most prominent features described was memory impairment, which led to the name amnesic shellfish poisoning (ASP). Domoic acid is produced by different species of *Pseudonitzschia* and other marine organisms, such as the red alga *Chondria armata*, and can potentially enter the food chain by contaminating shellfish, crustaceans, and other types of seafood. The most common vector is the blue mussel (*Mytilus edulis*). Although depuration occurs with time, harvesting and consumption of the shellfish at the time of contamination can lead to human or animal intoxication. Since this incident, specific control measures have been implemented in Canada and around the world to prevent food-borne illness associated with domoic acid in bivalves. Although these measures have been successful in preventing other episodes of ASP, there are reports of domoic acid intoxication in wild animals, including sea lions, whales, sea otters and sea birds, as well as reports of coastal water contamination in many world regions. Historical insight on recreational shellfish harvesters and the impact of domoic acid shellfish contamination indicates recreational harvesters, often-local aboriginal communities, such as those living on the Pacific coast in the US and Canada, are at higher risk of acute and chronic exposure to domoic acid and other algal toxins through contaminated shellfish. Warning and awareness are essential to the safety of recreational harvesters, as consumption of shellfish under these conditions may escape the safety net of surveillance testing. Furthermore, HABs appear to be increasing worldwide, including those of the *Pseudonitzschia* species, which produce domoic acid. This is having particular impact on the health of sea lions off the California coast. Two separate clinical syndromes are now described in these animals: one associated with acute domoic acid toxicosis, and a neurological syndrome characterized by epilepsy described as a consequence of chronic sub-lethal exposure to the toxin.

Domoic acid is one of the most potent excitatory amino acids (EAAs) and neurotoxins that can enter the food chain. It is a water-soluble tricarboxylic acid. Its potential toxicity is mitigated by its toxicokinetics: it is poorly absorbed by the gut, poorly penetrates the blood brain barrier (BBB) and has a very short half-life in most tissues compartments. Factors altering these parameters, such as a poorly developed BBB during brain development, age and pre-morbid pathology (e.g. renal diseases) have been identified as risk factors for domoic acid toxicity.

The acute toxic effects of domoic acid are well characterized. Recent publications review current knowledge relevant to health effects and mechanisms of action of domoic acid [3,5]. The cumulative evidence

supports the view that the developing nervous system is highly susceptible to the neurotoxicity of domoic acid. Sex differences and increased susceptibility to domoic acid toxicity of the developing brain have been demonstrated using rodent models, including exposure during pre-natal and early post-natal development. Toxicokinetic parameters leading to longer exposure during development have been implicated as risk factors for developmental neurotoxicity. Species differences, protective mechanisms and experimental route of exposure deserve special consideration when interpreting current data and in designing future studies, as most data were obtained using exposure through routes other than the oral, e.g., intravenous, intra-peritoneal, directly into cerebrospinal fluid. Data on sub-chronic or chronic oral exposure is limited [4,6,7]. Further investigations are required particularly developmental toxicity

The issue of exposure to domoic acid and epilepsy deserves special public health consideration because it is potentially a preventable cause of epilepsy in humans and because rapidly accumulating data from experimental studies and episodes of wildlife intoxication support a cause-effect link. The first evidence of domoic acid induced seizures was the 1987 episode of acute human intoxication, which provided strong support for the role of excitotoxicity in epileptogenesis. Seizures were among the neurological features, observed clinically and by electrophysiology, in association with this episode. A domoic acid-induced convulsion affects limbic structures such as the hippocampus and the entorhinal cortex, and different anatomic markers can detect these neurotoxic effects to varying degrees. Studies in rodents suggest that acute domoic acid exposure affects discrete brain circuits by inducing convulsions, with associated chronic functional and morphological effects on brain structures and on glutaminergic neurotransmission. Experimental animal studies with rodents and other species have served as the basis for the development of experimental models to study epilepsy, including preconditioning, acute seizure induction, and a chronic state of epilepsy. In vivo exposure of wildlife includes a neurological syndrome characterized by epilepsy described as a consequence of chronic sub-lethal exposure to the toxin.

Domoic acid research evolved from be the agent responsible of an unfortunate human intoxication event to be an important research tool providing new information and opening new avenues into the mechanisms of action of excitatory amino acids, excitotoxicity as a pathway of neural injury, glutamate receptors distribution within and outside the central nervous system, revelling potential targets for toxicity and pharmacotherapy, and the development of an experimental model to study epilepsy.

Domoic acid exerts its toxic effects through activation of glutamate receptors (GluRs) widely expressed in the central nervous system and other tissues [3,5,8-12]. Domoic acid induces excitatory toxicity (excitotoxicity) by an integrative action on ionotropic GluRs (iGluRs) at both sides of the synapse for which it has high affinity, preferentially the kainic acid (KA) subtype, coupled with an effect that prevents the channel from rapid desensitization. A synergistic effect of domoic acid with endogenous glutamate and N-Methyl-D-aspartic acid (NMDA) receptor agonists has been demonstrated in vitro and in vivo.

There are two main types of GluRs: ionotropic (iGluRs) form ion channels permeable to particular cations, and include: N-Methyl-D-aspartic acid (NMDA), 2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl (AMPA) and kainate receptors (KA), and metabotopic GluRs (mGluRs) activate intracellular signalling mechanisms via several associated G proteins. mGluR have been classified into Group I (mGlu1 and mGlu5 receptors), Group II (mGlu2 and mGlu3 receptors) and Group III (mGlu4, mGlu6, mGlu7 and mGlu8 receptors). There are differences in the potency of compounds that can activate glutamate receptors and their affinity for specific subtypes of the GluRs.

The neurotoxicity induced by excessive activation of GluRs known as excitotoxicity, is considered an important pathway of neural injury, and has been associated with acute and chronic neurodegenerative diseases such as amyotrophic lateral sclerosis, Alzheimer's Disease, Drug Addiction, Schizophrenia. Although GluRs were thought to be predominantly located in the CNS, it is now known that they are also present in peripheral neural and non-neural tissues where, unprotected by the blood-brain barrier, they are more readily exposed to exogenous excitatory amino acids (EAAs). GluRs in peripheral tissues are potential targets for the effects of EAAs present in foods, and could explain some of the clinical manifestations associated with these compounds, such as cardiac arrhythmia seen with domoic acid intoxication and with monosodium glutamate (MSG) in susceptible individuals. They may also be viewed as potential sites for drug development [8-12]. Further investigations are required on long-term effects of excitatory amino acids in food, particularly their mixtures, their potential synergistic effects, and conditions such as neurodegenerative disorders.

Despite of the advances made on domoic acid research, phycotoxins and HABs many gaps remain on their toxicity and/or beneficial effects, producing organisms, impact and interaction with the ecosystem, and factors influencing algal blooms such as climate change, pollution etc. International multidisciplinary collaboration is paramount to minimize harmful effects and to find beneficial uses of these compounds.

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