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CHEMISTRY, SOURCES, AND TOXICOLOGICAL ASPECTS OF DOMOIC ACID

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ABSTRACT

Domoic acid (DA) is a hapten, kainic acid and a potent neurotoxin. Upon exposure, it causes amnesic shellfish poisoning (ASP). The toxin is produced by microscopic algae, specifically diatomic genus known as *Pseudo-nitzschia*. DA is accumulated in shellfish, sardines, and anchovies. Poisoning results in human and other marine mammals, when they eat contaminated seafood. Toxicological symptoms of ASP involved epilepsy, headache, dizziness, confusion, short term memory loss, seizures, cardiac, respiratory, abdominal disorders, coma and possible death. ASP was characterized as a prolonged epileptic disorder after a series of pathological investigative studies in California sea lions over DA intoxication incidents between 1998 and 2006. This review extends the understanding of pathological aspects of DA toxicology.

KEYWORDS: Domoic Acid, Amnesic Shellfish Poisoning, Neurotoxin, Pathology, Sea Lion

INTRODUCTION

Harmful algal blooms (HABs) are caused by overgrowth of marine algae producing natural toxins which upon intake are extremely harmful for marine mammals (Figure 1), sea birds and ultimately to the human. They are a serious environmental problem worldwide. HABs are large collection of phytoplankton, microalgae and sometime heterotrophic protists present at the coastlines all over the world. The discoloration of the water due to over-abundance of these microorganisms leads to brown, green, mahogany or red tides respectively. The formation of blooms results surface scum and low oxygen due to increased respiration or decomposition. They also pose environmental threats such as mortalities, respiratory, digestive, neural, cardiac, integumentary disorders and vital resource losses at coastal regions i.e. aquatic vegetation and benthic epi- and in-fauna (Backer et al., 2015; Sellner et al., 2003).

Domoic acid (DA) is a potent neurotoxin and produced by marine diatomic genus of *Pseudo-nitzschia*. This toxin is a member of chemical group called kainates; it is a crystalline water-soluble amino acid. DA is predominantly found in various types of shellfish species, including numerous analogues have been found in marine samples, about 10 isomers of DA (isodomoic acids A – H and DA 5′ diasteriomer) (Wright et al., 1990; Zaman et al., 1997).

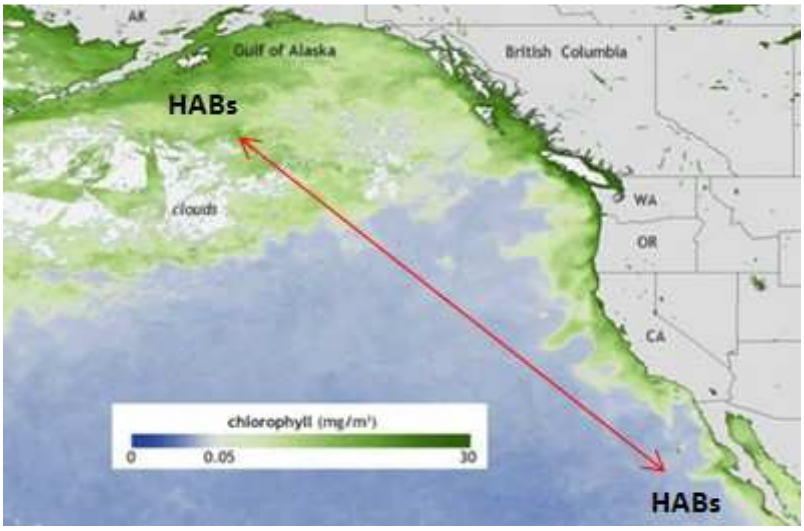

Figure 1: A Harmful Algal Bloom Stretched Across the Coastline of USA as Shown by the Red Arrow. The Green Color Shows High Concentrations of Chlorophyll Which is a Pigment Produced by the Algae

DA overdose in human results in behavioral disorder and epileptic disease which is characterized by spontaneous recurrent seizures from weeks to months with progressive recurrent seizures and behavioral abnormalities (Perl et al., 1990). Various studies have also reported epileptic disorder in California sea lion (Gull and et al. 2002; Pulido, 2008; Lefebvre and Robertson, 2010; Costa et al., 2010; Grant et al., 2010; Rams dell, 2007; Cendes et al., 1995; Goldstein et al., 2008; Muha and Rams dell, 2011; Fuquay et al., 2012; Pitkänen and Sutula, 2002; Sloviter and Bumanglag, 2013). The current study focuses on DAchemistry, sources and poisoning that lead to toxicity.

CHEMISTRY OF DA

It is a characteristic hapten, kainic acid analog neurotoxin and a proline (Figure 2); it has low molecular weight of 311.33034 g/mol and stable at room temperature. DA is denatured at high temperatures (>50 ^{o}C), at low pH (pH< 2) and high pH (pH 14) respectively. The sterilization of shellfish tissue reduce the total concentration of DA up to 3% (Johannessen, 2000; Quilliam, 2003; McCarronandHess, 2006; Bouillon etal., 2006).

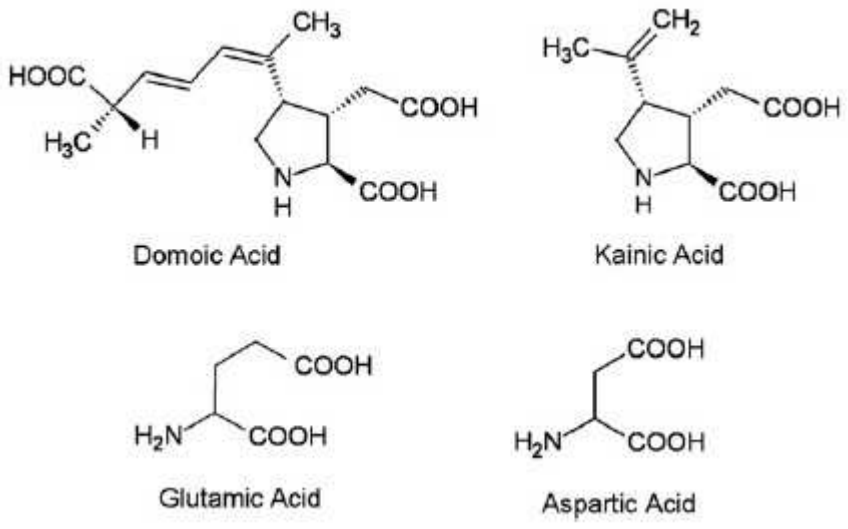

Figure 2: Chemical Structures of Domoic Acid and Related Amino Acids

SOURCES OF DA

DA is primarily produced by diatom *Pseudo-nitzschia*spp. (Bates et al., 1989). There are various species of this diatomic algae such as *Nitzschia navis-varingica* (ranges from tropical to temperate water) (Kotaki et al., 2000) and Nitzschia bizertensis(located in marine shores of Tunisia) (Smida et al., 2014). The other sources include macroalgae*Chondriaarmata* (TakemotoandDiago, 1958), *Chondriabaileyana*(Kotaki et al., 2000), and *Alsidiumcorallinum* (Impellizzeri et al., 1975).

Economic Effects

The coastlines have severely been damaged by overexposure to HABs. The shellfish harvesting (crabs and especially razor clams contaminated by DA) faces ban in the season of highly toxic marine environment due to the overgrowth of toxic marine algal species. The commercial crab industry is worth approximately $84 million annually at only one state of USA such as Washington. The damage due to these HABs has been estimated to be $9 million according to the NOAA at coastal areas of USA alone (Dough ton, 2015; K.G.W. 2015; Ahearn, 2015).

TOXICOLOGY OF DA

Mechanism of DA Action

DA mimics a powerful excitatory neurotransmitter called glutamate; this neurotransmitter is secreted by the neurons for signaling to other neurons and for the activation of the receptors. DA binds effectively to glutamate receptors which results in overexposure and ultimately cell death by degeneration. The specific neurons damaged by the excitation of DA make up hippocampus and the amygdala; these parts of brain are responsible for memory formation. Irreversible uncontrolled calcium inflow increases into the cell due to overexposure and excitation by the DA leads to the death (Figure 3) (Pulido, 2008).

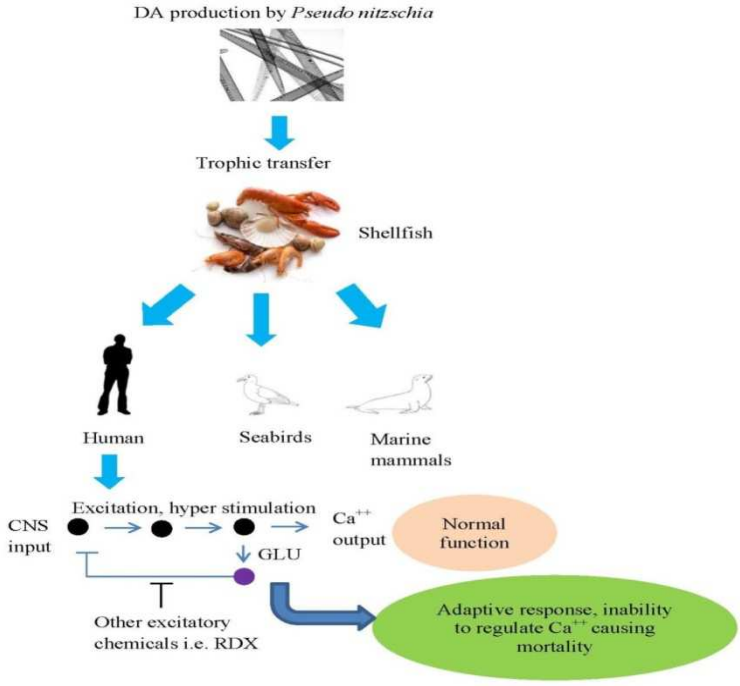

Figure 3: DA Causes Glutamate Induced Hyper Stimulation of Neurons in Human Nervous System Accumulating Excess Ca^{++} which Leads to the Death

ASP

DA poisoning was first reported in 1987 at Canada from the consumption of contaminated shellfish, 107 incidents were documented (eighteen percent hospitalized) and four deaths within 24 days (Perl et al., 1990). Gastrointestinal symptoms are developed within 24 h and neurological symptoms are developed within 48 h respectively. Severely affected individual experienced convulsive seizures, anterograde memory impairment, peripheral neuropathy, and altered metabolism in the temporal lobes (Teitelbaum et al., 1990; Teitelbaum, 1990).

Toxicology

DA poisoning with unidentified mortality of California sea lions (*Zalophuscalifornianus*) have been reported over multiple years. In 1998, 400 of these animals were found stranded due to DA contamination. The causal agent identified was *Pseudo-nitzschia australis* (Scholin et al., 2000; Torres et al., 2009). Clinical symptoms in intoxicated sea lions included ataxia and intermittent or continuous seizures for one week, this condition lead to recovery or death with treatment period (Gull and et al., 2002).

Clinical Pathology Findings

The disease progress after consumption of contaminated shellfish results in disorientation, gastric, neuro and nervous disorders. Gradually, the health status of intoxicated patient becomes worse with focal seizures leading to periodic epileptic discharges, abrupt impulse transmission as revealed by CT scan. Subsequently, amygdala, piriform cortex, thalamus, septum, olfactory tubercle, claustrum, nucleus and hippocampus are damaged severely at pyramidal cell layer other than H2 (*i.e.*, CA2). DA analogue kainic acid induces epilepticus syndrome in mice by attacking endogenous kainic acid receptors similar to the human TLE (Carpenter, 1990; Hauser and Hesdorffer, 1990; Nadler, 1991; Dudek et al., 2005; Vincent and Mulle, 2009).

BRAIN TOXICOLOGY

DA affects brain pathology by activating AMPA/kainite subtype of glutamate receptors. DA is water soluble and is readily dissolved in the plasma which is filtered through the kidneys. The estimated half-life of DA is 20 minutes, and when a Balb/c micewas exposed to DA, it only took four hours to clear from the plasma. Due to the characteristic solubility of the DA, it is poorly absorbed by the gut and released exclusively in the feces. DA mimics glutamate and thus activates the respective receptors; this activation leads to the excitotoxicity affecting the normal physiology of the brain structure and cellular damage. Essentially, DA binds to the glutamate receptors causing neurotoxicity in the central nervous system (CNS) being a chemical analogue of kainic acid. The area of the brain rich in kainic receptors affected by the structural damage is hippocampus which is specific for proper memory function (Hampson and Manalo, 1998; Suzuki and Hierlihy, 1993; Truelove and Iverson, 1994; Maucher and Rams dell, 2005; Iverson et al., 1989; Rams dell, 2007; Foster et al., 1981; Tyrphonas et al., 1990).

CONCLUSIONS

Diatomic marine algae are found globally and they are known to produce HABs, harmful toxins produced by these species pose a permanent threat to millions of human lives, seabirds and marine mammals. Several intoxication incidents by the consumption of contaminated sea food have been occurred at coastlines all around the world. DA is one of a potent neurotoxin produced by the genus of *Pseudo nitzschia* and travel through the food chain by the consumption of

contaminated shellfish. The toxin attacks glutamate receptors and kills the neural cells at the brain regions of hippocampus and amygdala thus leading to the memory loss, convulsions, epilepsy, gastric, cardiac, respiratory disorders and eventually death. Therefore, continuous monitoring is needed to check the unlimited growth of HABs and reducing the intoxication threat to animal and to the environment. The present study has revealed essential aspects of DA with a great deal of benefit to the readers to understand its importance in marine life and effects on human health which is continuously at risk to the marine toxins.

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Conflicts of Interest

The authors declare no conflict of interest.

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