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Neural Toxicology and Pathology of Domoic Acid

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Abstract
Domoic acid is a potent neurotoxin when intake via contaminated seafood in bulk quantity, results in neural tissue necrosis. It caused an outbreak of human poisoning in Canada in 1987 by the consumption of contaminated blue mussels (*Mytilus edulis*), produced by red alga *Chondria armataand* and the genus *Pseudo nitzschia*. Domoic acid targets the glutamate receptors and the poisoning was characterized by memory impairment and brain disorders which led to the name Amnesic Shellfish Poisoning (ASP). Domoic acid has intoxicated wild animals and contaminated coastal waters since the 1987 incident. Hence it poses a global health and safety threat to significant human and wild animal lives populated at the shorelines. The present review aims to extend the understandings of ASP, DA induced toxicology and pathology which are critical for human health and wildlife safety.
Keywords: Domoic Acid, Amnesic Shellfish Poisoning, Neurotoxicology, Neuropathology.

1. Introduction
Domoic acid (DA) was identified as potent neurotoxin which was responsible for Canadian 1987 human poisoning incident (Hynie *et al.* 1990; Todd, 1990; Liston, 1990; Perl *et al.* 1990; Quilliam, 1989; Iverson et al. 1989). It is produced by the genus *Pseudo nitzschia* (Bates et al. 2008; Bates, 2003; Kotaki et al. 1999; Amzil et al. 2001; Walz et al. 1994) and *Chondria armata* (Zaman et al. 1997). It infests the food chain by the consumption of contaminated seafood, the main seafood source is blue mussel (*Mytilus edulis*) (Lawrence, 1990; Johnson et al. 1990; Grimmelt et al. 1990), and other shellfish and crustaceans (Blanco et al. 2002; Powell et al. 2002; Wekell et al. 1994). It is a water soluble carboxylic acid containing hapten, poorly penetrates the blood brain barrier [BBB] and hinders the normal brain development, also cause renal diseases and have short life span in various tissues (Ramsdell, 2007; Iverson and Truelove, 1994; Preston et al. 1991; Wright et al. 1990; Iverson et al. 1990; Levin et al. 2006; Doucette et al. 2004; Jeffery et al. 2004; Hesp et al. 2007; Doucette et al. 2007; Truelove et al. 1994; Suzuki and Hierlihy, 1993; Wozniak et al. 1991). This study focuses at the understanding of toxicological and pathological effects caused by DA and its roles in brain physiological disorders.

1.1 Domoic acid chemistry
DA is a naturally occurring crystalline water-soluble acidic amino acid that has been isolated from macro- and microalgae and belongs to the kainoid class of compounds (Wright and Quilliam, 1995). DA can be purified by chromatographic methods and detected by UV spectroscopy at specific wavelengths. In 1987 incident, the source of DA was a diatome *Pseudo nitzschia* (formerly *Nitzschia*) *pungens* forma *multiseries*. DA is a class of excitatory neurotransmitters, cause depolarization of the neuronal cell by binding to specific cell receptors and continues until cell rupture occurs (Wright, 1995).

Geometrical isomers isodomoic acid A, B and C were investigated in *Chondria armata* (Figure 1), three other isodomoic acids D, E, F and C5' (Figure 1) were isolated from plankton cells and shellfish tissue (Wright and Quilliam, 1995; Ravn, 1995). Zaman *et al.* (1997b) isolated two new isomers of DA from *Chondria armata* i.e. isodomoic acid G and H, (Figure 1).

2. Toxicology
DA intoxicates a vast number of wild animals, including sea lions (neural tissue necrosis), whales, sea otters and sea birds (Lefebvre et al. 2002; Gulland et al. 2002; Lefebvre et al. 1999; Scholin et al. 2000; Sierra et al. 1997; Goldstein et al; 2008), followed by coastal water contamination due to ever increasing number of Harmful algal blooms (HABs) (Takahashi et al. 2007; James et al. 2005; Hess et al. 2001). This is having particular impact on sea lions health off the California coast (Goldstein et al; 2008). DA has been reported in the category of highly toxic marine haptens that target brain tissue involving specie variations and physiological disorders (Tiedeken et al. 2007; Burt et al. 2008; Adams et al. 2007; Burt et al. 2007; Bernard et al. 2007; Levin et al. 2006; Tiedeken et al. 2005; Levin et al. 2005; Doucette et al. 2004; Doucette et al. 2003; Xi et al. 1997). It can further infect the developing fetus by crossing the placental membranes (Maucher et al. 2007; Maucher et al. 2005). Hence DA is a global threat and its toxicology have been reviewed previously (Chandrasekaran et al. 2004; Jeffery et al. 2004; Ramsdell, 2007; FAO/IOC/WHO, 2004).

California sea lions (*Zalophus californianus*) mortality events with signs of neurological poisoning have been reported. In 1987, 400 sea lions were found beached onshore from Monterey Bay to San Diego and 70 animals were investigated (Scholin et al. 2000). The poisoning was correlated with *Pseudo nitzschia australis* blooms (Torres et al. 2009). Clinical signs included continuous seizures up to one week, ataxia, head weaving, seizures, or coma, followed by treatment-aided recovery or death (Gulland et al. 2002).

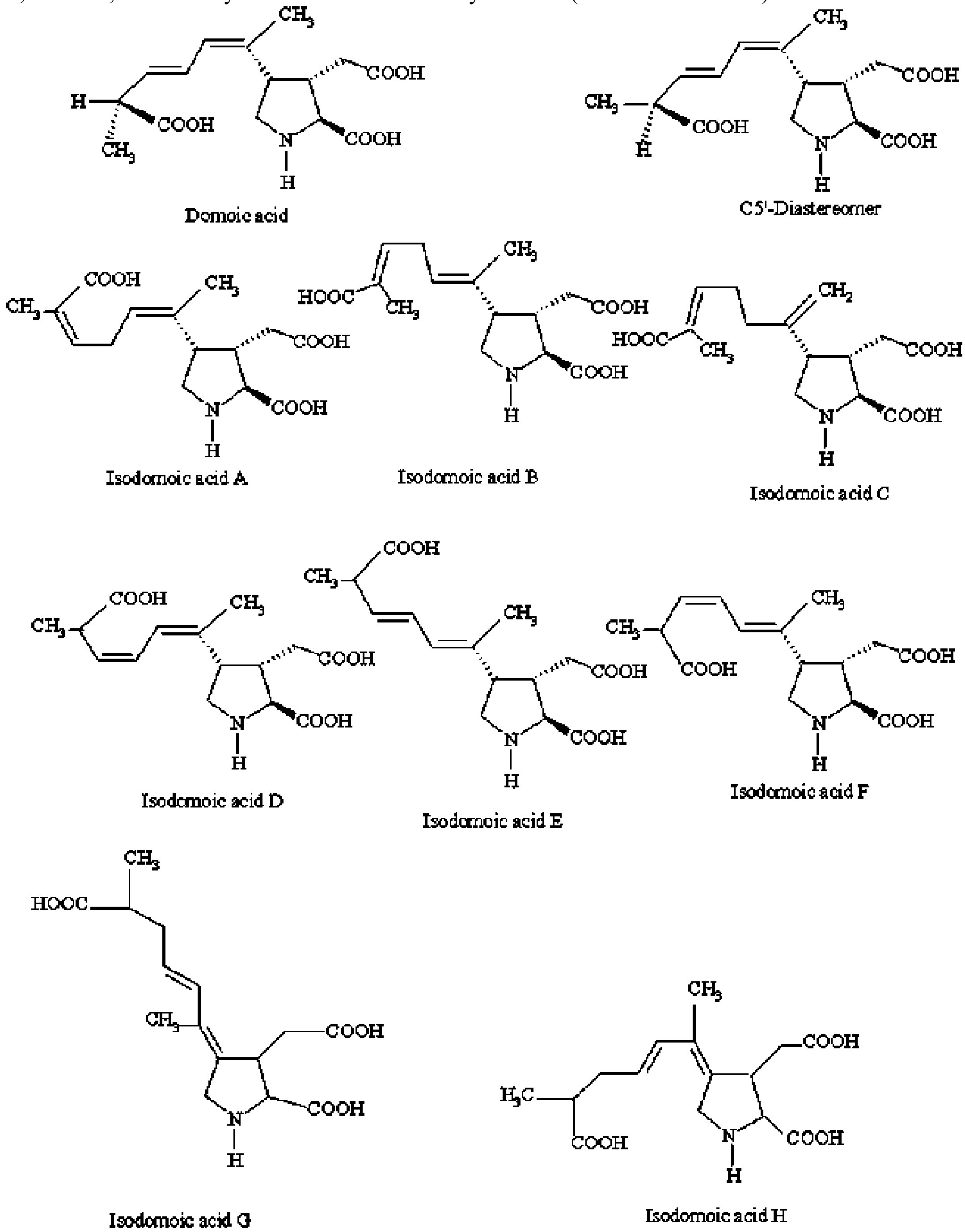

Figure 1. Domoic acid and its isomers chemical structures.

2.1 Toxicological Pathway

DA is structurally analogous to kainic acid (KA). Both of these haptens are analogues of glutamate (excitatoryneurotransmitter in the brain) which is responsible for the glutamate receptors (GluRs). DOM has high affinity to (GluRs) and induces excitotoxicity by effecting ionotropic GluRs (iGluRs) at both ends of a synapse which results in the prevention of the channel from rapid desensitization (Sawant et al. 2007; Hald et al. 2007) (Figure 2).

3. Clinical Pathology

3.1 Acute symptoms

The acute symptoms of ASP are inflammation in gastro intestinal tract, tissue necrosis in the central nervous system (CNS), followed by memory impairment physical disorientation, coma and in severe cases death. The symptoms are developed systematically in 48 hours in male older patients > 60 years, and in younger persons already suffering with diabetes, chronic renal disease and hypertension. The prominent feature termed was memory impairment which led to the name Amnesic Shellfish Poisoning [ASP] (Perl et al. 1990; Lefebvre and Robertson, 2010; Costa et al. 2010).

3.2 Amnesic Shellfish Poisoning

Amnesic shellfish poisoning (ASP) was first described from 11 November to 4 December 1987 caused by DA poisoning. The individuals established gastrointestinal symptoms within 24 h, i.e., vomiting and diarrhea, or neurological symptom within 48 h, e.g., confusion, memory loss, disorientation, or other major objective sign, such as seizures, coma, or cranial nerve palsies. Most severely poisoned individuals caught seizures and over an eight-week period became gradually normal (Perl et al. 1990).

3.3 Epilepsy

Three stage progression of DA poisoning to epileptic disease. A latent period of silent toxicity characterizes the transition between DA poisoning and epileptic disease. The continuum from exposure to disease can be described stepwise from early biological effect seen during the poisoning event to altered structure/function during the latent period to progressive damage that intensifies with the appearance of clinical disease (Cendes et al. 1995).

Epileptic disease (Figure 2) due to DA in the rat model initiates with (1) DA poisoning; its resultant (epileptic lesion) (2) structural damage that alters physiological functions (reorganization) and (3) progressive damage that exhibits the disease state (seizers) (Pitkänen and Sutula, 2002).

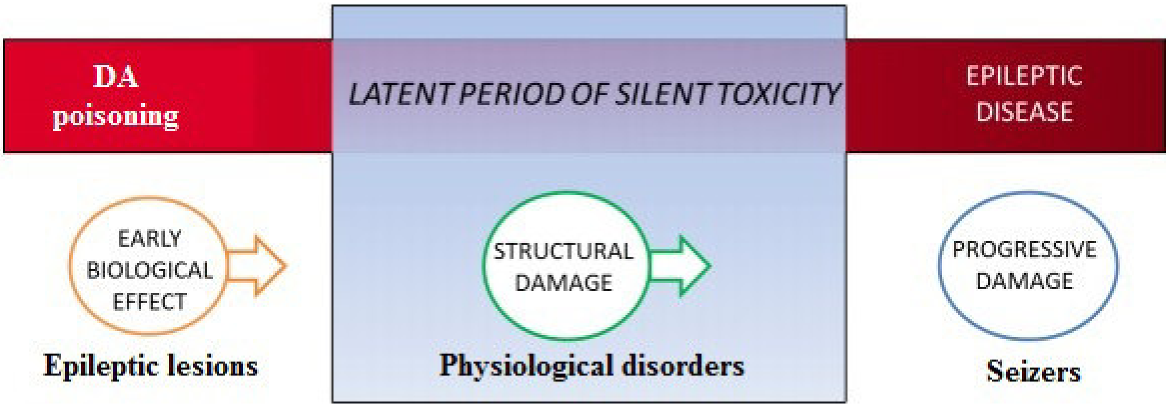

Figure 2. A rat model shows the three stage progression of DA poisoning to epileptic disease.

4. Brain Pathology

The DA tissues/cell injury shows similarities with brain ischemia, brain trauma and other excitotoxins, shares a common pathway for CNS and in peripheral tissues response as previously been demonstrated (Figure 3) in California sea lions (*Zalophus californianus*). The activation of GluRs causes neurotoxicity (Figure 4) with the release of endogenous glutamate leading to tissue injury (Ryan et al. 2005; Gagliardi, 2000; Kirchgessner et al. 1997).

Today we witness great advances in our understanding of glutamate neurotransmission, mechanisms involved in excitotoxicity, and their role on the pathology and treatment of a variety of diseases, including multiple sclerosis, stroke, chronic degenerative, neurologic disease and epilepsy. Here we provide an overview (Figure 3) of those aspects more directly relevant to DA induced pathology (Gagliardi, 2000; Doyle et al. 2008).

Figure 3. Damage to the hippocampus, DA poisoning has been shown in California sea lion. Left: a normal brain section. Right: Part of the brain that has been affected by DA exposure - shrunken hippocampus marks the tissue necrosis.

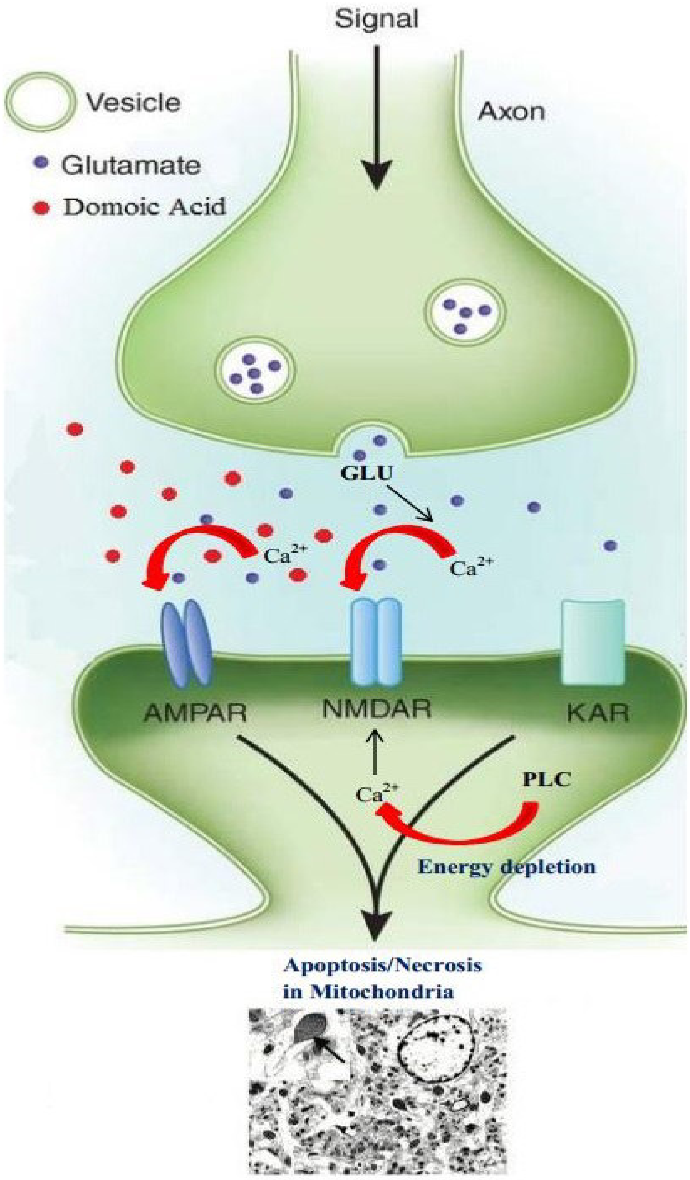

Figure 4. The pathological pathway of tissue degeneration shows over excitation of the brain cells.

5. Conclusions

Seafood is related with various foodborne ailments such as intoxications, sensitizations and infections. Marine biotoxins are of great importance to the seafood industry, because these naturally occurring toxins can move in to the food chain and induce toxicity. DA is of interest to public health worldwide because millions of human lives dwells the coastal shorelines and their health is at stake. The human poisoning chapter of 1987 established the basis for the monitoring of DA and the control of ASP. Data obtained revealed that the elderly are more susceptible to DA toxicity. Histopathology promises of the acute excitotoxicity with specific structural and physiological distribution. The prime targets of the DA are structures within the limbic system especially hippocampus and elicits tissue necrosis resulting in long term memory impairment. The present study exposes several gaps that will need further investigation and that are relevant to health risk assessment of DA in future. This review will aid in understanding the disease state, its relationship with brain physiology and the mechanism involved in dissemination and degeneration of the neural tissues.

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Conflicts of Interest
The author declares no conflicts of interest.

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