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Environmental roles and biological activity of domoic acid: A review

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ABSTRACT

Domoic acid (DA) is classified as a potent neurotoxin, an excitatory amino acid naturally produced by several diatom species belonging to the genus *Pseudo-nitzschia*. The molecule is excitotoxic in the vertebrate central nervous system, myocardium and other organs that contain glutamate receptors. The biggest risk of DA exposure for humans comes from the consumption of DA-contaminated shellfish. Algal blooms, including diatom blooms, are an excellent source of biomass for filter-feeding marine organisms, which makes the knowledge of DA occurrence quite relevant. In recent years, DA exposure has become more widespread due to the higher prevalence of toxigenic *Pseudo-nitzschia* blooms and increased human consumption of seafood. There is therefore an urgent need to update frequently the latest information on DA. Symptoms of having consumed high doses of DA are known but there are still significant gaps in knowledge of the health effects of chronic exposure to low levels of DA as well as of effective methods for removing DA from shellfish tissues. Here we summarize current knowledge about DA: its structure and biological activity, degradation in seawater, ecological and physiological roles, new producers, and risks of human exposure to high and low concentrations of this toxin.

Contents

1. Introduction

The increase in frequency and prevalence of periodic and sudden harmful algal blooms (HABs) in seawater has become a growing problem worldwide [1–5]. Marine HABs that produce phycotoxins are formed mainly by marine phytoplankton such as dinoflagellates and diatoms, which are capable of rapid growth in all geographical areas. These organisms produce a wide range of biologically active secondary metabolites, some of which have therapeutic potential [6] or toxic properties to humans and animals [7]. Algal blooms are an excellent source of biomass for filter-feeding marine organisms, which makes the knowledge of phycotoxin occurrence quite relevant. Such phycotoxins cause >60,000 marine mammal poisonings worldwide per year, with a mortality rate of 1.5% [8]. The bioaccumulation of these toxins in filter-feeding marine organisms, and their transfer to higher trophic levels, are a great threat to marine ecosystems, fisheries resources and human health [7,9]. The increased prevalence of phycotoxins also leads to large economic losses for finfish and shellfish farming [10]. Human poisonings induced by phycotoxins in shellfish or fish tissues are divided into the following six groups (types), based on their exerted effects: paralytic shellfish poisoning (PSP) [11], neurotoxic shellfish poisoning (NSP) [12], amnesic shellfish poisoning (ASP) [13–15], diarrhetic shellfish poisoning (DSP) [16], azaspiracid poisoning (AZP) [17] and ciguatera fish poisoning (CFP) [8,18,19].

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The primary aim of this review is to update and complete the information described in previous reviews on DA [10,20–24]. In recent years, DA exposure has become more widespread, accompanied by an increased frequency and intensity of toxic *Pseudo-nitzschia* blooms [10,20]. One recent example is the major toxic bloom occurring during May to August 2015, along most of the west coast of North America [25]. This, plus the significant increase in global consumption of shellfish [26,27], entails the need for frequent updates on DA, in particular relating to its sources and human health risks.

DA is the toxin responsible for ASP. The first documented episode of ASP occurred in eastern Canada in 1987, and was caused by the consumption of blue mussels (*Mytilus edulis*) containing the potent neurotoxin, DA. As a result of the poisoning, at least four people died and 143 were hospitalized. The symptoms of the poisoning included both gastrointestinal (vomiting and diarrhea) and neurologic effects (short-term memory loss, confusion, seizures, coma, and even death) [7]. The source of DA was the diatom *Pseudo-nitzschia multiseries*, which was the main food for mussels [13,28]. The impact of DA has also been observed among marine wildlife representing various trophic levels in the food web. This toxin was the cause of death or illnesses of many fish, seabirds, sea otters, sea lions and whales [8,10,29]. Therefore, DA and the organisms that produce this toxin have become the subject of intensive research, but information about DA is still incomplete [20]. Studies have shown previously unknown threats and novel syndromes caused by acute and chronic exposure to DA [30].

This review summarizes and encompasses 1) detailed structure and properties of DA; 2) the latest list of species able to produce DA; 3) possible ways of human exposure to DA; 4) degradation of DA in the environment; 5) available knowledge on the ecological roles of DA; 6) toxicology and new symptoms of amnesic shellfish poisoning; and 7) graphical mechanism of DA action in nerve cells.

2. Structure and stability of domoic acid

DA belongs to the kainoid class of compounds [31]. The full structure of DA, which was confirmed following total synthesis, was first presented by Ohfune and Tomita [32]. DA is a water-soluble, crystalline, non-protein amino acid with a molecular weight of 311 Da. It contains a proline ring, one imino group and three carboxyl groups (Fig. 1). The carboxyl groups are responsible for the high hydrophilicity and polarity of the molecule [33]. The chemical structure of DA is similar to that of another neurotoxin, kainic acid (KA), and to that of glutamic acid (Glu) (Fig. 1). DA has many derivatives, including iso-domoic acids (iso-DAs) (designated A through H) and 5′-epi-domoic acid [24,34]. Iso-DAs were first identified in the red alga *Chondria armata* [35]. Since the identification of Iso-DAs, the production of some of them has been confirmed in other marine diatoms, including *Nitzschia navis-varingica* [36], *Pseudo-nitzschia australis* [37] and *Pseudo-nitzschia seriata* [38]. Sometimes, a small amount of Iso-DAs is found in plankton cells and molluscan shellfish [31,39]. Iso-DAs also constitute degradation products of DA formed under exposure to UV radiation or heat [40,41] (see Section 4). Isomers are present in the environment at lower concentrations than DA. Moreover, the affinity of iso-DAs to the glutamate receptor is approximately 240 times lower than that of DA [39]. This lower affinity is related to the lack of the two conjugated double bonds between the 1′-2′ carbon atoms in the molecular structure of iso-DAs [42]. Therefore, iso-DAs are not a major threat to humans or animals, in contrast to the parent toxin [43]. Relevant physical and chemical properties of DA are summarized in Table 1.

Table 1
Physical and chemical properties of domoic acid [134,135].

IUPAC name	(2S,3S,4S)-2-carboxy-4-1-methyl-5(R)-carboxyl-1(Z)-3(E)-hexadienyl pyrrolidine-3-acetic acid
Empirical formula	$C_{15}H_{21}NO_6$
Molecular weight	311.33 g mol^{-1}
Density	1.273 g cm^{-3}
Absorbance maximum	242 nm
Solubility in water	8 mg mL^{-1}
Appearance	Finely crystalline white solid
Lethal dose	LD_{50} (intraperitoneal injection mouse) = 3.6 mg kg^{-1} LD_{50} (oral mouse) = 68 mg kg^{-1}

3. Producers of domoic acid

Originally, DA was isolated from the red seaweed *C. armata* and was used in Japan as an intestinal parasite remedy [6] and as an insecticidal compound [44]. Additionally, the ability to produce DA has been reported in other genera of marine diatoms, such as *Amphora coffeaeformis* [45] (although this finding has been disputed [46]), *N. navis-varingica* [47] and *Nitzschia bizertensis* [48] (Table 2). *Pseudo-nitzschia* is a cosmopolitan genus of pennate diatoms with at least one-third (19) of the species capable of DA synthesis, out of the 45 described to date [49]. *P. multiseries* [28], *P. australis* [50,51] and *P. seriata* [52] are recognized as major DA producers, which can produce even >10 pg DA $cell^{-1}$. Other species belonging to the genus *Pseudo-nitzschia* produce <1 pg DA $cell^{-1}$ [10,53]. The occurrence of toxic *Pseudo-nitzschia* species has been reported in many coastal areas on all continents, except Antarctica [20]. In polar regions, DA production has been confirmed only in Greenland, by *P. seriata*, in amounts of 1.46–1.93 pg DA $cell^{-1}$ [38]. Although toxic *Pseudo-nitzschia* species (e.g., *P. australis* [54], *P. calliantha*, *P. galaxiae*, *P. multiseries*, *P. multistriata* [55], *P. pseudodelicatissima* [56], *P. pungens* and *P. seriata* [10,52]) are found in European waters, neither mild cases of DA poisoning nor human deaths associated with DA have yet been reported [10,57]. The lack of DA poisoning may result from the low production of DA by the species present [58] or the lack of methods to detect the low concentrations of DA on the human body [30]. However, it cannot be assumed that mild cases of DA poisoning have not occurred [10].

4. Degradation of domoic acid

DA is stable for nine months in an aqueous acetonitrile solution at 20 °C [59] and for one year in an aqueous solution (pH 5–7) at 4 °C in the dark [20,60]. Long-term storage is best at −80 °C [60]. Decomposition is observed at high temperatures (>50 °C) [59], at extreme pH (pH 2 or 12) or during exposure to oxygen [60]. However, cooking shellfish products containing DA at 121 °C does not reduce its absolute concentration [61]. Any reduction in DA content in shellfish tissue during heating or freezing is caused by the translocation of hydrophilic toxin

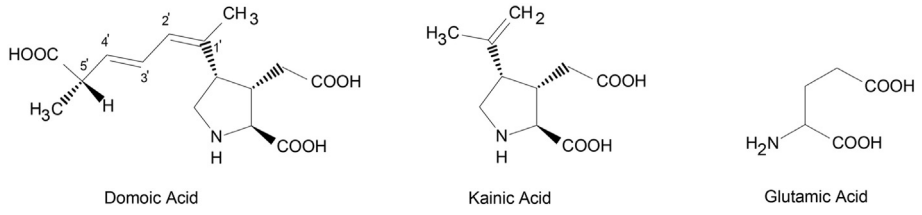

Fig. 1. Structures of domoic acid, kainic acid and glutamic acid.