What California sea lions exposed to domoic acid might teach us about autism: lessons for predictive and preventive medicine

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Abstract Autism spectrum disorder (ASD) shares many biological and behavioral similarities with the deleterious effects of domoic acid (DA) exposure. DA is produced by marine algae and most commonly by species of *Pseudo-nitzschia*. Humans and marine mammals can be exposed to DA when they consume whole fish or shellfish. The mammalian fetus is highly sensitive to the deleterious effects of DA exposure. Both ASD and exposures to toxic levels of DA feature repetitive behaviors, challenges with social interaction, and seizures. They can also share a commonality in brain anatomy and function, particularly the balance between excitatory and inhibitory mechanisms. The current article is relevant to predictive, preventive, and personalized medicine for three reasons. First, shellfish consumption may be a risk factor for ASD and the regulatory limit for DA should be adjusted to prevent this possibility. Human contributions to increased algal production of DA in coastal waters should be identified and reduced. Second, evaluations of sentinel species wild and free-roaming in the environment, though typically outside the purview of biomedical research, should be much more fully employed to gain insights to risk factors for human disease. To better identify and prevent disease, biomedical researchers should study wild populations. Third, studies of DA exposure highlight the possibility that glutamate additives to processed foods may also have deleterious impacts on human brain development and behavior.

Keywords Domoic acid · Autism spectrum disorder · Glutamate · Behavior · Anatomy · Brain · Development ·

Predictive diagnosis · Targeted prevention · Population screening

Autism and its prevalence

Autism spectrum disorder (ASD) is often diagnosed early in childhood and features deficits in social interaction and communication and includes repetitive behaviors and circumscribed interests [1, 2]. The prevalence of autism is more common among boys than girls [3] and has increased substantially over the past 20 years [3, 4]. ASD is the most highly heritable developmental disability yet researchers have identified only a few genetic susceptibility factors [5–10] that can account for a small fraction of the diagnosed population [10].

The role of environmental factors in the pathology of autism

The increased prevalence of ASD suggests an environmental contribution to its etiology. Part of the increased prevalence can be attributed to increased clinician awareness of the disorder and to diagnostic substitution [11–14] but the increase may also result from environmental changes, including a growing variety of pollutants that are ubiquitous in our environment [15, 16].

To the extent that exposures of chemicals in the environment vary with location, it can be helpful for scientists to identify variations in the geographic distribution of ASD. In this regard, the prevalence of autism is elevated along the coasts of Canada, the northern USA, and Korea [17–19], areas where human populations typically consume high levels of fish and shellfish [20, 21]. This geographical distribution suggests the possibility that exposure to toxic chemicals in seafood might contribute to the prevalence of some forms of autism. Indeed,

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persistent organic pollutants and heavy metals can be extremely high in seafood, especially fish high on the food chain. Also troubling is the growing prevalence in our seas of the neurotoxin, domoic acid (DA), which specifically targets brain functionality by its excitatory influence on neurons.

Toxicity of domoic acid

DA is produced by marine algae and most commonly by species of *Pseudo-nitzschia* [22]. Although the rapid increase in the presence of these marine algae along highly populated coastlines suggests that this change is a direct result of human influence on ocean chemistry, it remains unclear what factors specifically contribute to their rise. What is known is that DA accumulates in the viscera of filter-feeding fish and shellfish that live within areas where algal blooms produce DA.

Humans are exposed to DA when they consume the entirety of fish or shellfish (including the contaminated viscera), particularly clams, oysters, mussels, sardines, and anchovies [21]. Commercial processing of some shellfish, such as crabs, can promote leaching of DA from the viscera into the consumable muscle meat [23, 24].

Human consumption of contaminated fish and shellfish can result in amnesic shellfish poisoning (ASP). Depending upon the dose of DA and adult age, ASP presents with mild discomforts, such as gastrointestinal symptoms, and with progressively larger doses, memory loss, seizures, coma, or death.

Protection limits for DA were not designed to protect children

The regulatory limit for DA in seafood (20 mg/kg tissue) is designed to safeguard adults from acute exposures to DA that result in ASP [26]. Acute symptoms of ASP include memory loss, seizures, coma, and death [25]. The action limit of 20 mg/kg tissue would result in an intake of approximately 0.1 mg/kg DA /kg body weight, assuming a 300-g meal of mussels by a 60-kg human [27].

Critically, promulgated protection limits for DA in commercial seafood are not designed to protect children. Rodent studies indicate that young animals are substantially more sensitive [28, 29] than adults [30, 31] to the toxicity of DA, with one report showing a 40-fold difference between perinatal and adult sensitivity to DA toxicity [29]. Compounding this difference in sensitivity are data suggesting that prenatal exposure to DA might be greater than the exposure levels of the pregnant mother. DA can move across the placenta [32] and be transferred through mother's milk [33]. Levels of DA can become concentrated in the amniotic fluid and both fetuses exposed to DA *in utero* and pups exposed via breast milk are substantially more sensitive to this toxin than are rodents exposed in adulthood

[28–31]. After crossing the blood-brain barrier [32], DA binds to glutamate receptors expressed in several regions of the developing brain, including the cortical and limbic areas that regulate social behavior [34, 35].

The regulatory limit for DA is of particular concern for children born in the Pacific Northwest, Chesapeake Bay, and along the coasts of western Europe and eastern Asia, where peak annual levels of DA in shellfish occasionally exceed the regulatory limit, resulting in intermittent closures of shellfish harvests [36]. Further, since per capita shellfish consumption among shellfish consumers can be several fold greater than the average rate [37] and DA levels in mussels, oysters, Dungeness crab and particularly razor clams are at times just below (2–15 mg/kg) the regulatory limit, fetal exposures might at times far exceed average levels.

The toxic effects of DA share similarity with autism

DA is biochemically quite similar to the neurotransmitter, L-glutamate, a biomolecule that mediates signals within the brain. The mechanism of action is that DA promotes an increase in the level of excitatory tone between neuronal synapses in the brain [38], an imbalance that favors neuronal excitation over inhibition. When DA binds to neuronal glutamate receptors, the neurons become hyper-excitable. If these neurons become over-excited, they can die. This process is called “excitotoxicity.” The imbalance caused by DA exposure between neuronal excitation and inhibition can also promote seizure activity within the brain [39–42]. Further contributing to this imbalance, DA exposure can also be highly toxic to cortical GABA-containing interneurons [43–49]. Interneurons can downregulate neurological activity. These neurons also play a critical role in normal brain development.

Critically, when we think of excitotoxicity versus brain development, it is important to take into consideration that whereas high doses of excitotoxic chemicals might be required to kill fully developed neurons, much lower exposures during development can moderate the subtle variations in neuron excitation that direct brain development. These subtle changes in neuron excitability can have long-term effects on brain function.

The behaviors and neuropathology resulting from prenatal exposure to DA are strikingly similar to the behaviors and pathologies featured in ASD. Perinatal exposures to DA at levels far lower than those that cause mortality in adult rodents can cause long-lasting impairments in social behavior, which is the core diagnostic feature of autism [1, 2]. When rats are exposed to DA early in life, they are challenged by long-term deficits in social behavior, particularly males [50], a sensitivity that resembles the sex bias in autism. DA exposure and ASD also share commonality in the expression of repetitive behaviors [51, 52] and heightened seizure activity, which occurs in

approximately one quarter of autistic children [53–55]. Less obvious behavioral phenotypes that are shared by exposure to toxic levels of DA and ASD include deficits with spatial memory, which are expressed by both DA-exposed California sea lions and children with ASD [56, 57].

Indeed, exposure to toxic levels of DA and ASD share similarity in their increased brain excitatory tone [40, 41] and their aberrancies and impairments in interneuron structure and function [58–60]. Critically, variations in excitatory tone are associated with deficits in social functioning [61] and in heightened seizure susceptibility [54, 62–64]. Exposure to toxic levels of DA and ASD also share in common abnormalities in limbic structures [64, 65], particularly the hippocampus [66–69] and the amygdala [64, 70, 71], along with possible similarities in connectivity [72, 73]. Lesions in the hippocampus and amygdala are a prominent feature of autopsies from brains of DA-exposed humans, rodents, and DA-exposed marine mammals [64, 66, 67]. Structural anomalies in these brain regions are also common in autism [68, 69, 77].

Most previous studies have focused on the influences of DA exposure on the hippocampus because DA exposure is epileptogenic [38]. However, prenatal exposure to DA affects the development of cortical neurocircuits that are critical for the regulation of social behavior, such as the anterior cingulate cortex (ACC) [78], which plays a central role in empathic processing [79, 80], and the prefrontal cortex (PFC), which moderates sensory motor gating and the regulation of social behavior. Both the ability to experience empathy for distress [81, 82] and underlying activity of the cingulate cortex [83–85] are diminished in ASD.

DA binds with high affinity to the receptor GluK2 [86]. This receptor is highly expressed in the cingulate cortex of the newborn rat [35]. Particularly concerning is the possibility that DA interacts with glutamate receptors in the cingulate cortex during perinatal development and thereby contributes to autistic-like social impairments in adulthood.

Of note, specific drugs, such as mGluR5 antagonists, have promise as a cure for autism [74]. These antagonists have a long history of reversing the toxicity of kainic acid [75, 76], an analog of domoic acid, thus further supporting a mechanistic link between DA toxicity and autism.

Commonalities also include geographic relationships. High autism rates have been reported for coastal communities that are adjacent to marine environments with high levels of DA [18, 19, 87]. Levels that are not high enough to result in coma or death in adults might be high enough during development to alter social behavior in children. Infant rats exposed to DA express long-term social withdrawal as adults after they are exposed to levels of DA that are 100-fold lower than levels that cause amnesic shellfish poisoning in adults [50].

Because DA is a water-soluble chemical, its residues do not build up in human body fat. Thus, conventional efforts that search for associations between disease and chemical levels in

the body (e.g., PCBs, DDT) cannot be employed to approximate levels of human DA exposure. To determine whether coastal populations are at risk of exposure to DA, we need to more fully monitor how DA exposure affects coastal human and non-human mammalian populations.

The value of California sea lions as sentinel organisms of DA exposure

A critical impasse in biomedical research today is that laboratory animals studied in captivity can be poor models of human biological systems [88, 89]. Rodents and primates raised in laboratory cages lack the agency to make the everyday decisions. They lack the freedom to modify their environments or influence the nature of their experiences. Laboratory cages offer their inhabitants vastly diminished living spaces compared to what they are naturally designed to navigate in the wild. While the biology and behaviors of caged laboratory animals bear resemblance to those of humans, the full capacity of their biological systems is blunted when compared to the resilience and complexity expressed by free-roaming conspecifics [88]. We know, for example, that even a small increase in cage size can lead to vast changes in brain anatomy and behavior, changes that are likely the result of epigenetic responses to cage environments [89]. We also know that rodents under wild conditions express a more human-like subset of immune cells [90, 91] and vast changes in brain morphology [91].

In this regard, studies of the California sea lions (*Zalophus californianus*) have provided researchers with rare insight into the influences of a chemical exposure on the behavior of freely roaming animals. Since the early 1970s, increasing numbers of California sea lions have stranded along the Pacific coast of North America, most commonly as victims of acute exposure to DA [92]. They are exposed to DA via their consumption of prey fish, such as anchovies and sardines that can harbor toxin-producing algae in their viscera [93]. Lactating female sea lions are exposed to substantial levels of DA when they consume large numbers of prey to nurse their pups [93] and are at particularly high risk when they are restricted to foraging areas adjacent to rookeries where DA levels can be quite high [94].

Like with humans, sea lions display acute effects of domoic acid exposure that include obtundation, seizures, coma, and death [95]. Since DA is rapidly depurated and becomes undetectable in bodily fluids within 48 h of exposure [96], confirmation of acute exposure in sea lions requires necropsies to identify brain lesions in the hippocampus [64].

Chronic exposures are more common and symptoms are less obvious. Sea lions exposed to DA can express partial and

full seizures. More often, they express repetitive behaviors, such as chewing on flippers, swimming in tight circles, rocking along the floor, or head weaving. Indeed, the expression of repetitive behaviors can be predictive of DA exposure [97]. Sea lions exposed to DA can also exhibit periods of lethargy and inappetence and aggression towards other sea lions and humans, and they have been found to travel to unusual locations, including cities several miles inland or far away from the coast [98]. Many, if not most, die at sea.

California sea lions exposed to DA express biological and behavior phenotypes that resemble what is observed in the laboratory rodents and we can learn more from these aquatic species. California sea lions are exposed to a tremendous variety of transient and persistent toxic chemicals that more aptly resemble human exposures by contrast to the single toxicant exposures of laboratory animals. Parallels between the results of laboratory studies and observations of sea lions naturally exposed to DA give us a rare opportunity for independent substantiation that DA exposure may be a risk factor for ASD.

Critically, we should consider improving the laboratory animal models of this disorder. Mentioned earlier, rodents raised inside standard laboratory cages lack cognitive and affective challenges common in the wild and in human society. As a result, captive life inside a cage is likely to engender low or at least unnatural levels of neuronal excitation. With next to nothing to learn inside a standard lab cage, lacking any challenges to be overcome, this unnatural and modest level of neuronal stimulation could mitigate some of the potential for the hyper-excitatory effects of this neurotoxin. Recommended here is that future studies of the effects of DA exposure on rodents use complex home environment settings that allow research animals to roam freely in under naturalistic conditions that offer species-relevant challenges [88]. In these kinds of environments, we expect DA exposure have more pronounced excitotoxic effects.

Expert recommendations

We need to develop a regulatory limit for DA consumption that adequately safeguards the health of our most susceptible human populations. Research over the past two decades strongly indicates that early life stages of mammalian development are much more susceptible to the toxic effects of DA than are adults. The regulatory limits for consumption must be adjusted to protect children.

We need to think beyond regulatory limits for food consumption when we consider human health and well-being. There are tremendous benefits to personalized and targeted uses of medicine to optimize outcomes [99] but we must also take into account public health situations so large in scope that societal changes may be necessary to protect vast numbers of

human and non-human individuals. Native American populations in the Pacific Northwest consume high levels of shellfish and this diet is fundamental to their culture and livelihood [100]. Unnaturally high DA levels result, in part, from the wastes generated by our cities. In a sense then, we have an ethical responsibility to identify the human-generated factors that contribute to the increase of algal production of DA and we need to reduce these contributions. This is a social justice issue.

Second, studies of California sea lions have served as an essential foundation to our understanding of the pernicious effects of DA exposure. These sea lion studies highlight the value for preventative research in studying wild and free-roaming organisms. Wildlife studies are typically outside the purview of biomedical research but they can help us predict risk factors to human health. National institutions that fund biomedical research should support wildlife sentinel programs.

Lastly, the obvious parallels of DA toxicity with features of the autism diagnosis beg for more thorough examination of the neurotoxic contributions of all chemicals that bind to glutamate receptors. Indeed, glutamate is used commercially as a food additive and, like domoic acid, has excitatory influences on brain development and social behavior. We should fully explore whether glutamate additives are a risk factor for neurodevelopmental challenges in humans, such as autism.

Compliance with ethical standards

Ethical approval This manuscript represents a review of the literature and is not the direct result of studies of humans or animals. Prior studies in the author's laboratory on mice and California sea lions followed all applicable international, national, and/or institutional guidelines for the care and use of animals. The author declared that he has no conflict of interest.

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