# RAT KAINIC ACID MODEL PROVIDES UNEXPECTED INSIGHT INTO AN EMERGING EPILEPSY SYNDROME IN SEA LIONS

**Novel Symptomatology and Changing Epidemiology of Domoic Acid Toxicosis in California Sea Lions (*Zalophus californianus*): An Increasing Risk to Marine Mammal Health.** Goldstein T, Mazet JAK, Zabka TS, Langlois G, Colegrove KM, Silver M, Bargu S, Van Dolah F, Leighfield T, Conrad PA, Barakos J, Williams DC, Dennison S, Haulena M, Gulland FMD. *Proc Biol Sci* 2008;275(1632):267–276. Harmful algal blooms are increasing worldwide, including those of *Pseudo-nitzschia* spp. producing domoic acid off the California coast. This neurotoxin was first shown to cause mortality of marine mammals in 1998. A decade of monitoring California sea lion (*Zalophus californianus*) health since then has indicated that changes in the symptomatology and epidemiology of domoic acid toxicosis in this species are associated with the increase in toxigenic blooms. Two separate clinical syndromes now exist: acute domoic acid toxicosis as has been previously documented, and a second novel neurological syndrome characterized by epilepsy described here associated with chronic consequences of previous sub-lethal exposure to the toxin. This study indicates that domoic acid causes chronic damage to California sea lions and that these health effects are increasing.

## COMMENTARY

The kainic acid model of experimental epilepsy has yielded a detailed understanding of some of the processes involved in epileptogenesis and the generation of spontaneous recurrent seizures (1). When administered systemically or intracerebroventricularly in animal models, kainic acid produces an epilepsy syndrome similar to human temporal lobe epilepsy. Experimental animals treated acutely with kainic acid develop status epilepticus with seizure onset in the hippocampus. After a latent period of days to weeks, these animals begin to exhibit spontaneous, recurrent limbic seizures—the hallmark of the epileptic state (2). Much like the human syndrome, there are histopathological changes, including cell death in hippocampal subregions CA1, CA3, and the dentate hilus, with sparing of the dentate gyrus reminiscent of human mesial temporal sclerosis. In addition, axonal reorganization in the form of dentate mossy fiber sprouting is one factor that produces a hyperexcitable circuit underlying the seizure-prone state. Finally, animals develop a variety of behavioral and cognitive abnormalities that resemble human temporal lobe epilepsy. Kainic acid acts via glutamatergic ionotropic kainic acid and AMPA receptors to initiate an excitatory cascade that produces these neurological sequelae (3). This report by Goldstein et al. provides an unexpected, real-life context by which to view the kainic acid model.

Domoic acid and kainic acid are excitotoxic glutamate analogs with close structural and pharmacologic similarities. These compounds, first identified 50 years ago in algal seaweeds of Japan, were used initially to treat roundworm disease. In 1978, 103 individuals were poisoned by eating shellfish (harvested from Prince Edward Island, Canada) contaminated with domoic acid (4). The contamination originated from a rapidly increasing algal bloom (5). In the Canadian outbreak, affected individuals developed seizures, agitation, confusion, memory deficits, and gastrointestinal distress; a few people died. Histopathology demonstrated hippocampal sclerosis. One subject who survived the acute poisoning event developed complex partial seizures with hippocampal sclerosis a year later, supporting a role for excitotoxicity in epileptogenesis (6).

Laboratory studies of domoic acid induce features in rodents and primates that parallel human symptoms, demonstrating that this compound causes excitotoxicity and damage to neuronal pathways responsible for learning, spatial memory, and seizure generation (7). However, experimental research using domoic acid has lagged behind studies using kainic acid in terms of defining the spectrum of clinical sequelae and pathogenetic mechanisms.

Shifting offshore winds and ocean upwellings fueled by climate oscillations off the California coast have initiated a decade of harmful algal blooms that produce domoic acid. The first major event, occurring in 1998, caused glutamatergic excitotoxity resulting in status epilepticus, subsequent hippocampal damage, and mass mortality of California sea lions (8). Goldstein and coworkers examined the epidemiology of 715 California

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sea lions with clinical signs of domoic acid poisoning that were stranded between 1998 and 2006. The term stranded refers to the death of an animal or its inability to return to its natural ocean habitat as a result of poor health or injury. In the present report, the authors documented both acute and chronic domoic acid toxicity, providing evidence that the acute toxicity leads to chronic disease. Over this 8-year period, three-quarters of the surviving stranded sea lions exhibited acute domoic acid toxicosis, with seizures, ataxia, or coma. The remaining animals exhibited a novel chronic epilepsy syndrome, characterized by behavioral abnormalities and recurrent limbic seizures similar to that observed in laboratory rodents and humans with temporal lobe epilepsy. The number of stranded sea lions exhibiting chronic epilepsy increased each year after a major algal bloom, with an estimated 4-month lag time between acute events and appearance of chronic symptoms. Additionally, clinical observations revealed that a subset of 32 animals admitted for acute poisoning by domoic acid developed chronic epilepsy after a latent period in captivity of 16 to 85 days.

An epizootic, defined as an epidemic outbreak of disease in an animal population, has major health implications for multiple species. Together, the epidemiological and clinical findings implicate domoic acid in a wildlife epilepsy epizootic. Decades of kainic acid use in epilepsy research provide a rich source of information to understand this chronic neurological epizootic and its high lethality rates (9). The development of epilepsy after a latent period is typical of severe kainic acid poisoning, but large epizootics of late-term fetal poisoning also occurred in the sea lions (10). An unusually high degree of fetal brain maturation and slow amniotic fluid clearance of domoic acid enhance the potential for a form of in utero chemical kindling in fetal sea lions as a consequence of repeated algal blooms (11,12). The effects of kainic acid on memory and behavior also may provide a basis to better understand the unusual behaviors of domoic acid-exposed sea lions. As described by Goldstein et al., some affected animals exhibited bizarre behaviors, such as climbing onto a police car, walking along a road, and appearing in a field 100 miles inland. The sea lions also manifested repetitive behaviors and abnormal aggression toward conspecifics and humans.

Researchers studying harmful algal blooms have sought insight from biomedical and clinical research to explain symptoms observed in the natural environment off the California coast. They have designated the integration of data from both laboratory animals and the diseased sea lions with data from humans as a key element in their 10-year strategic plan for research and response (13). The kainic acid model of epilepsy provides a basic science foundation for understanding this emerging chronic marine disease. Reciprocally, the emerging domoic acid epilepsy syndrome in California sea lions offers new information to expand the relevance of the kainic acid epilepsy model beyond the laboratory, where it can be investigated in populations of individuals who are amenable to brain imaging techniques in a clinical setting. This phenomenon reinforces the interaction among environmental events (such as harmful algal blooms) and the health of both marine animals and humans, as is recognized in the Oceans and Human Health Act of 2005 (HR 4818).

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