Red Tide and Shellfish Poisoning: Toxic Products of Marine Algae

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"…Moses raised his staff and hit the water of the Nile. Suddenly the whole river turned to blood! The fish in the water died and the water became so foul that the Egyptians couldn't drink it…" Exodus 7:20-21

Abstract

Algae or phytoplankton are single-celled photosynthetic organisms that that make up the lowest trophic level of aquatic ecosystems. Of the thousands of species of marine algae, a small number are known to produce chemicals that are toxic to other organisms including fish, birds, marine mammals, and humans. Coastal occurrences of toxic algae have traditionally been called *red tides* due to the change in water color that they sometimes cause. But the term red tide is no longer sufficient to describe the causes or effects of toxic marine algae. As we are learning, marine toxins produced by algae have a variety of sources, pathways, and receptors. One pathway common to several marine algal toxins is by human consumption of contaminated shellfish. Bivalve mollusks such as clams, scallops, oysters, and mussels that filter feed on toxic algae can accumulate large amounts of toxins in their tissues, posing a toxic threat to humans who make shellfish a part of their diet.

Four distinct types of human shellfish poisoning have been identified. These are descriptively named paralytic shellfish poisoning (PSP), amnesic shellfish poisoning (ASP), neurotoxic shellfish poisoning (NSP), and diarrhetic shellfish poisoning (DSP). The symptoms from these syndromes can vary from mild abdominal cramping to severe neurological disorders caused by lesions in the central nervous system. Death is possible, although not extremely common, in the most severe cases of PSP and ASP. In the last several decades, there has been a dramatic increase in the occurrence of events associated with marine toxins. Some believe the increase is only a perception, a reflection of our improvements in monitoring and diagnosis. Others, however, believe that the recent prevalence in marine toxins is being affected by human activities such as pollution, which increases nutrient loading in coastal waters. Given the potential threat to human health and economic loss, modeling, predicting, and controlling the occurrence of toxic marine algae events is a growing area of intense scientific research. Programs that monitor toxins in shellfish food supplies have proven successful at limiting shellfish poisoning in the United States, Canada, and Europe. Expanding these programs to other parts of the world would further diminish the threat of marine toxins to human health.

Introduction

Phytoplankton are microscopic, single-celled plants which use sunlight as the primary energy source for growth. Also called algae, these primary producers make up the foundation of the food web and are the eventual food source of higher forms of life that feed on them either directly or indirectly. Of the thousands of species of marine phytoplankton, roughly a few dozen are known to produce chemicals that are highly toxic to other animals, including humans (Anderson 1994). The toxic effects of marine algae can be manifested in a variety of different ways, depending on the specific toxin, pathway, and biological endpoint. This leads to some general confusion with terms and mechanisms of toxicity and makes it useful to summarize the causes and effects of marine algal toxins.

"Red Tide" is the term commonly associated with a massive multiplication or “bloom” of toxic algae. The name comes from the phenomenon by which pigmented phytoplankton reproduce to such high concentrations that the water visibly turns a red or dark brown color (Anderson 1994). This term can be somewhat misleading as red colored waters can also be caused by many species of nontoxic algae. Additionally, most occurrences of toxic marine algae are not accompanied by any visible change in the color of the water. Lastly, the occurrence of red tide has almost nothing to with ocean tides. Although somewhat of a misnomer, "red tide" is the term most frequently used to describe the causes or effects of toxic marine algae. In an effort to clarify the terminology, the scientific community has coined the broader term 'Harmful Algal Blooms' with HAB as the acronym. This term is also a misnomer but is nonetheless gaining popularity in common and scientific parlance. These algae have developed

adaptations that make them less susceptible to predation by zooplankton and other grazers. The fact that they sometimes happen to be toxic to our species is a matter of circumstance and makes them no more “harmful” than grizzly bears or rattlesnakes. With humans perhaps being the one notable exception, the term “harmful” shouldn’t be used to describe organisms and the adaptations they have developed to ensure their survival.

Background

Most toxic algae are classified as dinoflagellates with a few also being classified as prymnesiophytes and chloromonads. Dinoflagellates are unicellular, eukaryotic organisms that have two flagella (Fukuyo 1989). The primary means of reproduction of these organisms is by simple asexual fission, in which one cell grows large enough and divides into two cells, which in turn divide into four cells and so forth. With the necessary nutrients and sunlight, algae populations can rapidly increase to very high concentrations. Some blooms of these phytoplankton can result in concentrations as high as hundreds of thousands of cells in a single milliliter of seawater (Anderson 1994). The toxins produced by these algae can have significant toxicological effects on an inordinate number of other organisms.

Blooms of toxic algae near shore can cause localized airborne contamination. The combined action of waves, wind, and boat propellers volatilizes and disperses toxins into the air, causing mild respiratory problems for humans who breathe it. Symptoms common during red tides include a dry choking cough and a burning sensation in the eyes, nose, and throat. However, the airborne spread of algal toxins

does not pose a great health risk to humans and the symptoms usually disappear shortly after exposure is discontinued (Henry 2000).

Finfish can also be susceptible to marine toxins. As fish swim through a concentrated algae bloom, the fragile algae may rupture and release neurotoxins onto the gills of the fish. These neurotoxins then enter the fish's bloodstream, causing rapid death. In Florida, single large blooms of the dinoflagellate *Gymnodium breve* have killed hundreds of tons of fish in a day (Yasumoto 1993). Farmed fish are particularly vulnerable to marine toxins since the caged fish cannot avoid algae blooms as wild fish frequently appear to do. Fish that are exposed to lower concentrations may accumulate these toxins in their body and pass them on to higher trophic levels as they are preyed upon.

Toxic algae can also kill marine mammals and birds. In 1987, 14 humpback whales died in Cape Cod Bay, Massachusetts during a one-month period. It was determined that all of the whales had recently eaten mackerel. The mackerel's diet had included smaller fish and other zooplankton that had consumed large amounts of the dinoflagellate *Alexandrium tamarense,* which produce powerful toxins (Anderson 1994). In 1996, toxins produced by *G. breve* killed approximately 10% of the endangered population of Florida manatees. Because both the stomach contents and lung tissue contained the toxins, it is believed that the toxins entered through ingestion as well as inhalation (Anderson 1994). In 1991, more than 100 pelicans and cormorants were found dead or suffering from unusual neurological symptoms in Monterey Bay, CA. The cause of death was believed to be a bloom of *Psuedo-nitzcschia australis*, a diatom that produces the toxin domoic acid. The toxin was found in Northern anchovies, a major

part of the diet of the birds (Todd 1993). In a similar case, the bioaccumulation of neurotoxins in fish is believed to be the cause of the 1987 mass death of 700 bluenose dolphins (Todd 1993). These mass deaths of marine wildlife often cause public sadness accompanied by questions and misunderstandings as to whether or not this is “natural.”

Bivalve shellfish such as oysters, clams, and mussels feed exclusively on phytoplankton that they filter from seawater. Shellfish are usually unaffected by toxic algae themselves but can accumulate toxins in their tissue to levels that can be lethal to humans. The most serious threat posed to human health by marine toxins is through shellfish contamination. Four distinct types of shellfish poisonings have been identified. These are described as amnesic, neurotoxic, paralytic, and diarrhetic shellfish poisoning, abbreviated as ASP, NSP, PSP, and DSP respectively. Each of these syndromes is caused by a different species of toxic algae and has different mechanisms of toxicity and unique symptoms. Ciguatera fish poisoning (CFP) is a related seafood poisoning also caused by a dinoflagellate but will not be discussed in this text, which will be limited to red tide and shellfish poisonings.

Discussion

Paralytic Shellfish Poisoning

Of all types of seafood poisoning, paralytic shellfish poisoning (PSP) poses the greatest threat to public health and fatal cases have been reported around the world. PSP is caused by a group of about 12 structurally similar neurotoxins classified as saxitoxins, produced by several species of dinoflagellate organisms including *Alexandrium tamarense*, *Gymnodinium catenatum,* and *Pyrodinium bahamense* (Yasumoto et al 1993). Paralytic shellfish poisoning of humans is caused by the

consumption of shellfish that have been contaminated with saxitoxins. PSP has been found in North American shellfish from Alaska to Mexico, and from Newfoundland to Florida. The most notorious cause of PSP on the west coast of North America is *Protogonyaulax catenella*, and *Gessnerium monilatum* on the east coast (Yasumoto et al 1993).

The effects of PSP are primarily neurological and very fast acting, with the onset of symptoms occurring 5 to 30 minutes after the ingestion of the contaminated shellfish. It usually starts as a tingling numbness in and around the mouth that spreads to the face and neck. In severe cases, the numbness spreads to the arms and legs and causes loss of coordination and difficulty breathing. Depending on dose, these symptoms may subside or worsen to include difficulty swallowing, throat constrictions, and complete loss of speech. Other symptoms may include headache, nausea, vomiting, giddiness, dizziness, and loss of sight. Very severe cases result in complete paralysis and death from respiratory failure unless artificial respiratory support is administered. In non-lethal cases, the victim begins to gradually recover after about 12 hours and has no effects lasting longer than a few days (Anderson 2000). Incidentally, the symptoms of mild cases of PSP are similar to those caused by organophosphate pesticide poisoning.

Saxitoxin is a neurotoxin that inhibits the permeability of cell membranes to Na^+ ions. It does so by tightly binding to receptor sites near the external orifice of the sodium channel. This prevents Na^+ ions from passing through the membranes of nerve cells, interfering with the transmission of nerve signals. The result is the inability to control muscle functions. Saxitoxins are tetrahydropurines that are heat and acid stable,

therefore contaminated shellfish are no less toxic cooked than raw (Yasumoto et al 1993). The overall fatality rate for one group of PSP outbreaks ranged from 8.5 – 9.5%, indicating consistent concentrations of the toxins in the shellfish. A 1987 outbreak of PSP in Guatemala had a fatality rate of 14%, possibly indicating a lack of medical services. In this same outbreak, exposed children had a 50% fatality rate, indicating a greater sensitivity of children to saxitoxins (Anderson 2000). In mice, the saxitoxin LD50 is 3-10 μg/kg intraperitoneal and 263 μg/kg orally. Humans are roughly 10 times more sensitive than mice to oral doses of saxitoxins with death occurring at an oral dose of between 1 and 4 mg (corresponding roughly to 20-40 μg/kg), depending on age and physical condition (Anderson 2000). The disparity is attributed to the human's longer, more specialized digestive tract with greater potential for absorption.

There are no antidotes available for victims of PSP and medical care is usually limited to supportive therapy and respiratory support for severe cases. Drinking several glasses of water mixed with activated charcoal is recommended first aid for suspected cases of PSP. This may help minimize the amount of toxins that are absorbed by the system. As a public health threat, monitoring the amount of toxins present in shellfish beds and closing them to harvest as necessary generally control PSP. The most reliable method for measuring the amount of toxins in shellfish is by a mouse bioassay. In the US, beds of shellfish having greater than 800 μg/kg of specific toxins are closed to harvest. This amount is approximately 10 times lower than the lowest levels associated with cases of human poisoning (NIEHS 2000).

PSP is associated with relatively few reported outbreaks, most likely because of the effective control programs that prevent human exposure to toxic shellfish. That PSP

can be a serious public health problem, however, was demonstrated in Guatemala in a 1987 outbreak in which 187 cases with 26 deaths resulted from the ingestion of a clam soup (NIEHS 2000).

Amnesic Shellfish Poisoning

The most recently discovered seafood toxicity, amnesic shellfish poisoning (ASP) first appeared in 1987. In this outbreak, 153 cases of acute intoxication were reported in individuals who had eaten mussels harvested from Prince Edward Island, Canada. Most of these cases experienced gastrointestinal distress and many older persons also had neurological effects that included memory loss and dementia. Three cases resulted in death. This is a brief account of how ASP was first characterized.

Over a period of a few days in late November 1987, hospitals in the Montreal and Quebec areas admitted several elderly patients all suffering from gastroenteritis, confusion, and memory loss (Todd 1993). Questioning the patients on recent foods eaten, health authorities found that they had all eaten mussels. Samples of mussels associated with these cases were obtained and government laboratories began testing the suspect mussels using the standard mouse bioassay procedure used in testing for PSP toxins. In the mouse bioassay, mice were given intraperitoneal injections of extracts from suspect mussels and then observed for a period of up to 24 hours. Mice injected with extracts from contaminated mussels exhibited an uncontrolled scratching of both shoulders with their hind legs 7-21 minutes after injection (Todd 1993). This behavior was unique and unprecedented in previous PSP mouse bioassays. The mice then became uncoordinated, had seizures, and most died within 3 ½ hours. All the extracts from mussels associated with cases of human poisoning resulted in mouse

deaths and it was quickly confirmed that the mussels linked to the poisoning episodes had all been cultivated in the Cardigan River estuary on eastern Prince Edward Island (Todd 1993).

Because of the unique symptoms in the human victims and distinct mouse bioassay results, it was recognized early in the outbreak that the toxin was one not previously associated with shellfish poisoning. An analytical working group was quickly formed to isolate the new and baffling toxin. Working with government and university laboratories, the working group tested the mussels and found no significant levels of heavy metals, polychlorinated biphenyls, polynuclear aromatic hydrocarbons, or pesticides. An examination of the digestive tract of the mussels showed very low levels of 4 species of dinoflagellates in amongst a dominant amount of the diatom *Nitzschi pungens*. Diatoms are microscopic one-celled or colonial algae of the class *Bacillariophyceae* that have cell walls made of silica. Approximately one month from the first poisoning, Canada's Atlantic Research Laboratory determined the toxin to be domoic acid, an amino acid with a molecular weight of 311 g/mol. *Nitzschi pungens,* ingested by the mussels during their normal filter feeding, had produced the domoic acid.

Domoic acid is an analog of glutamic acid, an excitatory neurotransmitter that acts on the central nervous system (CNS) (Todd 1993). Domoic acid can be up to 100 times as potent as glutamic acid and exposure to high levels of domoic acid causes an excitatoxic action at receptor sites leading to excess neural excitation, neural seizures, and eventually lesions in the CNS. Domoic acid poisoning in humans and mice has

resulted in lesions in the amygdala, hippocampus, hypothalamus, olfactory system, retina, and anterior horn cells of the spinal cord (Todd 1993).

In order to understand the dose-response relationship of this newly discovered toxin, work was done to determine the amounts of domoic acid ingested by victims of this outbreak. In ten cases, the amount of mussels consumed was determined and leftover mussels were analyzed for domoic acid. A clear dose response relationship was found. Oral doses ranged from .2 mg/kg for an unaffected individual to 4.2 mg/kg for a case with severe neurological effects (Todd 1993). Subsequent testing of mussel extracts on cynomolgus monkeys gave symptoms similar to what humans experienced at similar oral doses. Bioassay testing showed that mice could tolerate oral doses up to 50 mg/kg without adverse effects (Todd 1993). This disparity is also attributed to the primate's longer digestive tract with greater ability to absorb this toxicant.

The three cases of ASP that resulted in death were in elderly people (aged 71-84 years). The brains of these patients showed severe physical damage. Loss of memory is attributed to lesions in the hippocampus, one area of the brain associated with memory. Of 12 severe but nonfatal cases, eight of the victims were older than 65 years. The other four had preexisting illnesses including diabetes, chronic renal failure, and hypertension. Many of the victims showed signs of selective short-term memory loss up to one year after the exposure. In one severe case, the individual still had selective memory loss five years after the incident (Todd 1993).

The prevalence of amnesic shellfish poisoning is currently quite small. Aside from the large initial outbreak, no additional cases of human poisoning have been reported. This is due in part to thorough paralytic shellfish poisoning (PSP) monitoring programs,

which also detect ASP. Recently, domoic has been found in many other places. In September 1991, domoic acid found in anchovies in Monterey Bay, California caused the death of large numbers of brown pelicans and cormorants, indicating that finfish as well as shellfish can vector domoic acid (Todd 1993). In 1998, domoic acid was implicated in the death of over 400 sea lions off the central California coast. Domoic acid has also been found in razor clams and Dungeness crabs in British Colombia, Washington, and Oregon (Anderson 2000).

Neurotoxic Shellfish Poisoning

The dinoflagellate *Gymnodinium breve* is the cause of red tides in the Gulf of Mexico and Caribbean. It was first recorded in 1880 on the west coast of Florida and continues to occur there on a frequent basis (Henry 2000). Blooms of *G. breve* have caused episodes of mass fish and bird mortality, human respiratory illnesses, and a milder shellfish poisoning called neurotoxic shellfish poisoning (NSP).

G. breve produces a group of neurotoxins called brevetoxins, lipid soluble polyethers with molecular weights about 900 g/mol (Yasumoto 1993). NSP is caused by the consumption of shellfish contaminated with brevetoxins produced by *G. breve.* The human neurological symptoms of NSP usually include false temperature sensations, muscular aches, dizziness, and anxiety. These are usually accompanied by gastrointestinal distress such as vomiting, diarrhea, and abdominal pain. No deaths have been caused by NSP and recovery is usually complete within a few days (Anderson 2000).

Brevetoxins act by disrupting the flow of Na+ ions in nerve cells. They bind to sites near the voltage gated sodium channels, allowing an unchecked flow of Na+ ions

into or out of the cell. This disruption of ion flow within nerve cells is responsible for the neurological effects associated with NSP. Incidentally, brevetoxins have nearly the opposite effect as saxitoxins, which bind to a different site and effectively block Na+ ions from passing through the sodium channel (NIEHS 2000).

Diarrhetic Shellfish Poisoning

Diarrhetic shellfish poisoning (DSP) is caused by eating shellfish contaminated with toxins produced by dinoflagellates of the genus *Dinophysis*. Symptoms usually occur 30 minutes to 12 hours after eating contaminated shellfish and include some form of gastrointestinal distress. Approximately 90% of the cases experience diarrhea and other symptoms may include nausea, vomiting, abdominal cramps, and chills (NIEHS 2000). No deaths by DSP have been reported and full recovery of even the most severe cases is usually experienced within a few days. DSP was first reported in the Netherlands in the 1960s and cases of DSP have since gained prevalence in Europe, Japan, and South America. In one of the largest outbreaks, over 5000 people experienced DSP in Spain in 1981 (NIEHS 2000).

Okadaic acid is the toxin responsible for DSP (Yasumoto et al 1993). The mechanisms by which okadaic acid causes diarrhea are not well understood but it is generally believed that it is a potent inhibitor of protein phosphatases. This probably causes diarrhea by stimulating the phosphorylation that controls sodium secretion by intestinal cells (Yasumoto et al 1993). Okadaic acid is also known to affect the flow of Ca^{2+} ions across cell membranes and some evidence shows that it promotes cancerous tumor growth in mice (Yasumoto et al 1993).

Conclusion

Although red tides have been recorded as far back as biblical times, reported cases of toxic marine algae are becoming increasingly more common around the world. Many scientific experts believe that the scale and complexity of toxic algae blooms have made an unprecedented expansion in just the last two decades (Anderson 1989). In the mid 20th century, only a few isolated regions were affected. Now every coastal US state is threatened by at least one type of algal marine toxin. While some believe this is only a reflection of improved surveillance and monitoring, there is general agreement that the problem of marine toxins is increasing. Remaining are the scientific and public debates as to whether humans have caused this expansion and whether humans have the ability to control it. Just a few of the explanations given for the recent rise in marine toxins include:

1) Natural species dispersal via currents.
2) Species dispersal via ship ballast water, fish farming, or shellfish farming.
3) Natural or human induced changes in global temperatures, climatic trends, and weather patterns.
4) Increased nutrient loading of coastal waters caused by pollution and other human activities.

There is some evidence for all of these hypotheses. One striking example of natural dispersal began in 1972. A red tide that stretched from Maine to Massachusetts appeared for the first time following a hurricane. This same red tide has now appeared there every year since (Anderson 1994). In other places, the increase in red tides and

outbreaks of shellfish poisoning has risen with the population. Between 1976 and 1986, the population of Hong Kong increased by a factor of 6. During the same time period the number of observed red tide events increased by a factor of 8 in the adjacent Tolo Harbor (Anderson 1994). It is speculated that along with the population growth came an increase in nutrient loading from pollution discharged into the harbor. A similar pattern was noted in the Inland Sea of Japan, where red tides increased steadily from 44 to over 300 events per year in a period of a decade. Effluent controls were instituted in the mid-1970's, resulting in a 50% reduction in the number of red tides (Anderson 1989). As our understanding of marine biology improves, so will our understanding of the causes of toxic marine algae blooms. There are currently many substantial efforts dedicated to tracking and eventually controlling algae blooms. Using methods including remote sensing and satellite imagery, researchers are trying to develop complex models and data sets that will help understand, predict, and eventually control the occurrence of toxic algae blooms. Methods being investigated for actively controlling red tides include:

1. Floating booms such as those used to contain oil spills.
2. Flocculation with clay to remove algae from affected coastal waters.
3. Biological control using predators such as zooplankton to control algae populations.

The use of these controls may find some success in the future and will only be limited by our wisdom to implement them. But not until we have a more solid understanding of the dynamics of marine algae populations will there be any success controlling them. Additionally, phytoplankton make up the very foundation of all marine food webs and efforts to control or eliminate them may have profound and unanticipated

effects on the structure of marine ecosystems. As with many perceived problems of an ecological nature, the symptoms may exist in one place while the cause is in another. Our wisdom in distinguishing the two is certainly limited and treating for the symptoms may actually cause a new and even larger problem. Waging an all out war on toxic species of marine phytoplankton, as some are doing, will be costly and likely futile.

Human poisoning by contaminated shellfish is not a pandemic global problem that poses grave health risks to humans as a whole. The typical year will see relatively few deaths or severe illnesses caused by eating contaminated shellfish. Nevertheless, shellfish poisoning is a persistent and annoying problem that regularly affects consumers of seafood, a large portion of the population in some areas. Monitoring of shellfish supplies for toxins has proved very successful in limiting human shellfish poisoning in developed countries and this monitoring should be continued and expanded to lesser-developed nations as possible. Efforts to minimize coastal pollution and the associated nutrient loading that it causes should also be continued. This will not only reduce the threat posed by marine toxins but also promote greater health and sustainability for our valuable marine ecosystems.

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