Natural Toxin

Toxins Passed from Animals to Humans

The action of natural toxins has long been recognized and understood course of human history. It is important to know the distinction between toxicant and toxin. A toxicant is any chemical, of natural or synthetic origin, capable of causing a deleterious effect on a living organism. A toxin is a toxicant that is produced by a living organism. All toxins are toxicants, but not all toxicants are toxins. Toxins, whether produced by animals, plants, insects, or microbes, are generally metabolic products that have evolved as defense mechanisms for the purpose of deterring or killing predators.

Aquatic biotoxins

Fig1: Contaminated Bivalve with toxins

There are two main types of aquatic biotoxins: algal toxins and ciguatoxins.

Toxins formed by algae in the ocean and fresh water are called algal toxins. Algal toxins are generated during blooms of particular naturally occurring algal species. Shellfish such as mussels, scallops and oysters are more likely to contain these toxins than fish. In general, shellfish predominantly bivalve shellfish like oysters, scallops and mussels ingest toxin-producing algae, toxins can build up in their tissues. If the shellfish that is contaminated with high levels of algal toxins is consumed it can lead to serious and potentially fatal illness. The algal toxins can be retained in shellfish and fish or contaminate drinking water. They have no taste or smell, and are not removed by cooking or freezing.

The consumption of seafood contaminated with algal toxins results in six different syndromes, paralytic shellfish poison (saxitoxins), neurotoxic shellfish poison (brevetoxin), amnesic shellfish poison (domoic acid), or diarrhetic shellfish poisoning (okadaic acid and related compounds), and ciguatera fish poisoning (ciguatoxin and other toxins) and scombroid poison (histamine). All except histamine are accumulated in shellfish or fish through the food chain from dinoflagellates, diatoms, or bacteria. All these organisms are phytoplanktonic or benthic forms of life, naturally occurring in specific areas of the marine environment.

Paralytic shellfish poisoning (PSP)

Fig2: Harmful Algal Bloom

PSP is caused by the consumption of molluscan shellfish contaminated with heterocyclic guanidines called saxitoxins. Currently, over 21 known saxitoxins are produced by dinoflagellate species. Toxicity is caused by binding of guanidines to voltage-dependent sodium channels, which blocks neuronal activity. The primary site of action in humans is the peripheral nervous system. Symptoms of toxicity include tingling and numbness of the perioral area and extremities, loss of motor control, drowsiness, and incoherence. Ingestion of 1–4 mg saxitoxin has resulted in death from respiratory paralysis.

Outbreaks

Outbreaks of PSP have occurred worldwide, due to the fact that saxitoxin-producing species of dinoflagellates can live in either temperate or tropical waters. Although shellfish poisoning outbreaks are more common in warmer months, toxin levels can be high enough to cause illness at any time of year. There are numerous outbreaks of PSP all around the world even in cold countries like Norway and Canada. We only introduce a few of them. In Portugal, after the 2007 outbreak, severe contamination with PSTs occurred again in 2008 and 2009, followed by the absence or weak short-lived contamination episodes during the following years. In early autumn 2018, contamination with PSTs increased in the centre and southwest of the Portuguese coastline, and a very sharp increase in just a couple of weeks was observed in some cases. The high toxin levels attained in some commercial bivalve species from the Lisbon and Setubal coasts, originated prolonged harvest bans which lasted until December 2018 or later, such as the bans applied to clams or blue mussels.

Diagnosis

The diagnosis of PSP based only on the recent consumption of shellfish and the development of clinical manifestations is difficult and can be inaccurate because these findings are nonspecific and similar to other diseases. In such cases, laboratory diagnosis using human samples can provide crucial information. Enzyme-linked immunosorbent assays (ELISA) are a

preferred screening tools because these assays can be performed rapidly, are accurate and sensitive.

Prevention Plan

PSP is prevented by large-scale, proactive monitoring programs and rapid closures of harvest in areas containing dinoflagellate algal blooms. Saxitoxins are not inactivated by cooking, and must be mitigated at their source to prevent ingestion. In the United States, the permissible level of saxitoxin equivalents in shellfish is 80 micrograms/100 grams.

Amnesic shellfish poisoning (ASP)

Fig 3: Amnesic shellfish poisoning- Harmful Algal Bloom

Amnesic shellfish poisoning (ASP), also known as domoic acid poisoning (DAP) because amnesia is not always present, was first recognized in 1987 in Prince Edward Island, Canada. At this time, ASP caused three deaths and 105 cases of acute human poisoning following the consumption of blue mussels. The symptoms included abdominal cramps, vomiting, disorientation and memory loss (amnesia). The causative toxin (the excitatory amino acid domoic acid or DA) was produced by the diatom species *Pseudo-nitzschia pungens* f. *multiseries P. fraudulenta P. turgidula P. australis*.

In September 1991, the unexplained deaths of pelicans and cormorants in Monterey Bay, California were attributed to an outbreak of DA poisoning produced by a related diatom *Pseudo-nitzschia australis*. This diatom was consumed by anchovies that in turn were eaten by the birds. In October 1991, extracts of razor clams from the coast of Oregon were found to induce DA acid-like symptoms in mice. These incidents prompted the regulatory authorities in the United States to conduct a massive survey of many marine species for the presence of DA. The toxin was found widely from California to Washington, and was also found unexpectedly in crabs, the first time this toxin was demonstrated in a crustacean. Since these incidents, global awareness of DA and its producing sources has been raised.

ASP is caused by domoic acid produced by diatoms of the genus Pseudo-nitzchia, which are consumed by mussels, scallops, clams and crabs. Domoic acid is a water-soluble, tricarboxylic amino acid that is a structural analog of the neurotransmitter glutamate and is a glutamate

receptor agonist. Persistent activation of the kainite glutamate receptor causes an increase in intracellular calcium, which can cause neuronal cell death and lesions of the brain where glutamineric pathways are concentrated. Areas of the brain involved in learning and memory processing are particularly susceptible. The symptoms of ASP are gastroenteritis, dizziness, disorientation, lethargy, seizures and loss of short term memory. Respiratory difficulty, coma and death may ensue . Human toxicity has occurred after ingestion of 1–5 mg/kg domoic acid

Prevention of ASP intoxication: Depuration

ASP are not inactivated by cooking, and must be mitigated at their source to prevent ingestion. To date there have been no useful methods devised for effectively reducing phycotoxins in contaminated shellfish. All methods tested have been unsafe, too slow or economically unfeasible, or have yielded products unacceptable in appearance and taste. Mussels were reported to take up DA rapidly but also depurated rapidly, while other bivalves retained DA for longer periods. Depuration of DA by razor clams is a long-term process. Depuration of DA from starved mussels and clams was relatively rapid (43 to 15 mg/g at 13 °C in 24 hours with traces remaining for up to six days in Passamaquaddy Bay, Canada, and 130 to 20 mg/g at 15 °C in four to six days in the Cardigan River, Canada). Complete depuration, however, in the natural habitat may take longer.

Whole scallops flesh contaminated with DA, showed a 43 percent decrease (mostly in hepatopancreas) in DA content after 180 days of frozen storage (-20 °C). During frozen storage, there was a transfer of DA from the hepatopancreas to the rest of the body, with a net average decrease in the whole product. Subsequently pickling of the scallops flesh or packing with brine and canning after frozen storage did not cause a further decrease of the DA content.

In laboratory studies, showed that DA was effectively depurated from the hepatopancreas of Dungeness crabs over a three-week period once the toxic feeding of DA via contaminated clam meat ceased. Depuration proceeded at a faster rate when crabs were fed toxin-free clam meat than when they were starved.

Preventive measures

Commercial harvest areas and aquaculture facilities are adversely and often unpredictably affected by toxic blooms. One problem is that certain algal species, which have never occurred in a certain area, may suddenly appear and then rapidly cause problems. Therefore preventive measures can hardly be taken. Extensive monitoring of the marine environment and the possibly contaminated fishery products together with regulations will be required to prevent (shell)fish poisoning incidents. Toxin concentrations in the fishery products can also vary with the species of fishery product involved and with the area of harvest. Harvested fishery products containing too much toxin were usually destroyed. Toxic doses are often estimated from left-over toxic seafood but these may not be always representative of the ingested food

Diarrhetic shellfish poisoning

Fig 4: Diarrhetic shellfish poisoning

Diarrhetic shellfish poisoning (DSP) is caused by the production of okadaic acid and dinophysistoxins in the dinoflagellates Dinophysis fortii or Prorocentrum lima, which are consumed by mollusks. Okadaic acid and dinophysistoxins are inhibitors of serine/threonine phosphatases, critical components of signaling cascades that regulate a number of cellular processes involved in metabolism, ion balance, neurotransmission and cell cycle regulation compared to other types of shellfish poisoning.

The symptoms of DSP are relatively mild, and generally consist of diarrhea, abdominal cramps, nausea, chills or vomiting within 30 minutes to a few hours after consumption of DSP toxins. Symptoms generally resolve within 2–3 days, with or without medical treatment. Diarrhea is most likely due to the hyperphosphorylation of proteins (including ion channels) in the intestinal epithelia, resulting in impaired water balance and fluid loss. The long term consequences of low level exposure to DSP toxins may be more serious, as they have been shown to be tumor promoters. The FDA has established an action level of 0.2 ppm okadaic acid plus 35-methyl okadaic acid (DXT 1).

Prevention of DSP intoxication: Depuration

The rate of DSP toxin loss varies with the season. It appears that low water temperatures retard toxin loss; however, the degree to which temperature affects the uptake and release of toxins is unknown. The rate of detoxification is highly dependent on the site of toxin storage - that is toxins in the gastrointestinal tract are eliminated much more readily than toxins bound in tissues. Information concerning bivalve molluscs reared in aquaculture showed that retention time of the toxin in Mytilus edulis varied from one week to six months.

The rate of removal of DSP toxin from shellfish (depuration rate) most likely depends upon the species and may be affected by such interrelated factors as feeding or pumping of the shellfish, temperature, salinity and the level of non-toxic algae and particulates. In Japan, DSP toxins decreased from 4.4 to 2.5 MU/g (by mouse bioassay) in one week and then to 0.5 MU/g by the next week. In the Netherlands, toxicity in mussels was no longer detectable by rat bioassay after four weeks at water temperatures of 14 to 15 °C .

All methods tested until now (generally tested for reducing PSP toxins such as transfer of shellfish to waters free of toxic organisms for self-depuration, vertical displacement of mussels in the water column as a means of minimizing toxin accumulation, ozone treatment of the water, temperature or salinity stress, electric shock treatments, reduced pH or chlorination, cooking) appeared to be unsafe, too slow, economically unfeasible or yielded products unacceptable in appearance and taste. Only after very rigorous boiling (163 minutes at 100 °C) toxin denaturation occurs.

Preventive measures

The prevention of shellfish-borne diseases requires monitoring of the marine environment and shellfish flesh. Frequent inspection of seawater around aquaculture facilities or shellfish farms for the presence of toxin producing strains of phytoplankton is an approach that is gaining support in several countries, and has received considerable impetus following the discovery that toxin-producing algae have been transferred in the ballast water of ships to completely new marine. The principal strategy to prevent DSP intoxication is effective monitoring of mussels with respect to DSP toxins so that contaminated products do not reach the market.

Ciguatera poisoning (CFP)

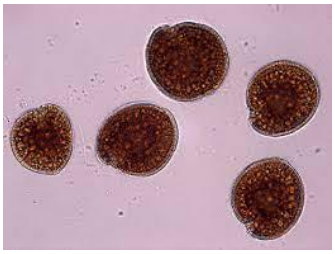

Fig 5: Ciguatera poisoning

The term “cigua” was somehow transferred to an intoxication caused by the ingestion of coral reef fishes. Ciguatera fish poisoning is caused by the dinoflagellate Gambierdiscus toxicus, which grows on filamentous macroalgae associated with coral reefs. The lipophilic precursors to ciguatoxin are bio-transformed to ciguatoxins in herbivorous fish and invertebrates that consume the macroalgae, and bioaccumulate in large carnivorous fishes associated with coral reefs. The causative toxins, the ciguatoxins, accumulate through the food chain, from small herbivorous fish grazing on the coral reefs into organs of bigger carnivorous fish that feed on them. High ciguatoxin concentrations may be found in barracuda, snapper, grouper and jacks.

Ciguatoxins are lipid-soluble polyether compounds consisting of 13 to 14 rings fused by ether linkages into a most rigid ladder-like structure. They are relatively heat-stable molecules that remain toxic after cooking and exposure to mild acidic and basic conditions. Ciguatoxins arise from biotransformation in the fish of precursor gambiertoxins. Ciguatoxins are structurally related to the brevetoxins and compete with brevetoxin for binding to the same site on the

voltage-dependent sodium channel. However, because ciguatoxin has a higher binding affinity for the site than brevetoxin, the toxic potency of ciguatoxin is higher than that of brevetoxin. The threshold level for toxicity in humans is estimated to be 0.5 ng/g. CFP is estimated to affect over 50,000 people worldwide each year.

The symptoms of CFP generally include gastrointestinal disturbances (nausea, vomiting and diarrhea) within 2–6 hours, followed by neurologic symptoms such as numbness of the perioral area and extremities, a reversal of hot/cold temperature sensation, muscle and joint aches, headache, itching, tachycardia, hypertension, blurred vision and paralysis. In rare cases, CFP is fatal. Inasmuch as ciguatoxin is produced by organisms that live beneath the surface and is not routinely monitored for concentration in seafood, the only way to prevent consumption is to completely abstain from ingesting tropical reef fish, as the occurrence of toxic fish is sporadic, and not all fish of a given species or from a given locality will be toxic [153]. Currently, there are no FDA regulations limiting levels of ciguatoxins in fish, although a recent publication suggests an advisory level of 0.1 ppb pacific ciguatoxin equivalent (P-CTX-1) toxicity values in fish from the tropical Atlantic, Gulf of Mexico, Caribbean, and 0.01 ppb P-CTX-1 equivalent toxicity in fish from Pacific regions. The mechanism of action of ciguatoxins is related to its direct effect on excitable membranes.

Prevention of CFP intoxication: Depuration

Ciguatoxin cannot be identified by odour, taste or appearance. It is also temperature stable so cooking or freezing will not destroy it. Ciguatoxin can also not be eliminated by salting, drying, smoking or marinating. The contaminated fish can remain toxic for years, even on a nontoxic diet. Apart from the avoidance of consumption of large predatory fish, the use of animal screening tests is the only tools presently available to prevent intoxication.

Preventive measures

The major source of ciguatera cases has been the fish caught by sport fishing (79 percent). If people could be educated to avoid consuming heads, viscera and roe of reef fish, and avoid fish caught in the areas known for frequent occurrence of ciguatoxin intoxication, the incidences of ciguatera probably would decrease dramatically.

Large predatory reef fish are most likely to be affected; the larger the fish, the greater the risk. Some authorities advocate avoiding fish that weigh more than 1.35 to 2.25 kg but this is only a relative precaution. However, there is no way of knowing the size of fish from which the steak or filet was cut. Organ meats, including the roe, appear to contain higher concentrations of toxins and should be avoided. Consuming small portions from several fish per meal instead of a large portion of any suspect fish will reduce the risk too.

Neurotoxic Shellfish Poison (brevetoxin)

The dinoflagellate Karenia brevis produces brevetoxins that are lethal to fish, but not to mollusks such as oysters, clams and mussels. Therefore, they can accumulate in healthy-appearing mollusks to concentrations that are toxic to humans who ingest them. Karenia brevis brevitoxins cause the syndrome known as neurotoxic shellfish poisoning (NSP), which affects sodium transport in the autonomic nervous system and causes inhibition of neuromuscular transmission in skeletal muscle. NSP is usually a relatively mild. NSP symptoms usually occur within a few hours of ingesting contaminated shellfish and may include abdominal pain, nausea and vomiting, vertigo, malaise, generalized muscle weakness, ataxia, incoordination, chills, headache, myalgia, a reversal of hot/cold temperature sensation and progressive parasthesias. dilated pupils, bradycardia and convulsions may occur in cases of severe poisoning.

Scombroid poison

Fig 6: Scombroid poison

Scombroid poisoning is a common form of food poisoning related to fish ingestion. Scombroid poisoning occurs after the ingestion of fresh, canned or smoked fish with high histamine levels due to improper processing or storage. First described in conjunction with fish in the suborder Scombroidea, it has since been described with other dark-fleshed fish (e.g., sardines and anchovies). Scombroid poisoning is one of the most common causes of morbidity associated with fish intake It is produced through the decarboxylation of the histidine to histamine in certain fish, notably tuna, mackerel, mahi mahi, and marlin, through bacterial spoilage. All these seafood toxins are resistant to normal cooking practices and are not detectable by o

Symptoms of scombroid poisoning include flushing, rash, urticaria (generally widespread erythema, usually lacking wheals), palpitations, headache, dizziness, sweating, and burning of the mouth and throat. Gastrointestinal symptoms can include abdominal cramps, nausea, vomiting and diarrhea. Bronchospasm, respiratory distress and vasodilatory shock have also been described. Symptoms begin within 10 to 90 minutes after eating the implicated fish. The rash lasts 2–5 hours, and the other symptoms usually disappear within 3–36 hours.

Histamine does not change the smell or appearance of the affected fish. Scombroid poisoning is frequently misdiagnosed. Because histamine does not alter the organoleptic quality, the fish may seem normal. However, elevated histamine levels can occur in fish owing to improper

refrigeration before processing or to storage of the fish at room temperature after cooking. Therefore, the appearance, taste and smell of the fish are poor guides as to the presence of histamine. Histamine is heat-stable and remains present after cooking, freezing, canning or smoking. Outbreaks are most common in summer.

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