Introduction

Tetrodotoxin (abbreviated as TTX) is a powerful neurotoxin found in a variety of animals and is responsible for upwards of 50 human fatalities a year. Captain James Cook was the first to record TTX poisoning in western literature in 1774 following an incident caused by ingesting fish from the family Tetraodontidae (commonly known as puffer fish). Incidents of poisonings in China due to consumption of puffer fish have been dated as far back as 2000 years.

Structure and properties

TTX, produced by bacteria or dinoflagellate species, is an alkaloid substance with a guanidinium group (including three nitrogen atoms, blue in Figure 1), a pyrimidine ring (red in Figure 1) and five other ring systems. It is a thermostable, non-protein and it is soluble in water.
Mechanism of action

TTX acts on both central and peripheral nervous systems. Also, it depresses the respiratory and vasomotor centers in the brain’s medulla oblongata. The guanidinium group of TTX prevents sodium diffusion by binding to voltage-gated, sodium channels of nerve membranes. This blocks the extracellular opening pores of the channel, nerves are not able, therefore, to conduct messages eventually causing paralysis and death.

Toxicity of TTX

As little as 1-2mg of purified TTX is lethal to an adult man of 75kg. Compared to potassium cyanide, TTX is 1000 times more toxic to humans and there is no known antidote.

Tetrodotoxin in Nature

Puffer fish, from which tetrodotoxin was first isolated in the early 1950s, was thought to be the only carrier of TTX. However, over the years, several independent studies have identified the neurotoxin in a wide array of phylogenetically distinct marine organisms (for example, goby fish, horseshoe crabs, xanthid crabs, the blue-ringed octopus, gastropods, starfish, flatworms, ribbonworms, arrowworms, annelids, red calcareous alga, and some dinoflagellate) and in a small group of amphibians (for example some salamanders, newts, and frogs). In these organisms (depending on the species) TTX has been isolated from eggs as well as such body parts as liver, gonad, skin, muscle, intestine, salivary glands, and digestive glands of various organisms.

Ingesting liver from certain species of puffer fish has led to TTX poisonings in humans. Food poisoning due to TTX was reported in Taiwan after consumption of goby fish as well. Also, incidents of poisoning following consumption of TTX-bearing horseshoe crab eggs have been recorded.

Table: TTX-bearing organisms

<table>
<thead>
<tr>
<th>Organism</th>
<th>TTX-rich organs</th>
<th>Records of Human poisoning</th>
</tr>
</thead>
<tbody>
<tr>
<td>Puffer Fish</td>
<td>liver, gonad, skin</td>
<td>Yes</td>
</tr>
<tr>
<td>Goby Fish</td>
<td>skin, viscera, muscle, testis</td>
<td>Yes</td>
</tr>
<tr>
<td>Horseshoe Crab</td>
<td>eggs</td>
<td>Yes</td>
</tr>
<tr>
<td>Xanthid Crab</td>
<td>appendages, cephalothorax,</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>visceræ</td>
<td></td>
</tr>
<tr>
<td>Blue-ringed octopus</td>
<td>salivary glands</td>
<td>No</td>
</tr>
<tr>
<td>Newts</td>
<td>eggs, skin, muscle</td>
<td>No</td>
</tr>
<tr>
<td>Frogs</td>
<td>eggs, skin</td>
<td>No</td>
</tr>
</tbody>
</table>

Production of TTX

While some studies maintain that production of TTX in animals is endogenous, others argue that the TTX-bearing organisms do not necessarily produce TTX themselves.

Isolation of TTX from a wide range of phylogenetically unrelated organisms, and the regional, seasonal, or individual variations in the levels and toxicity of TTX contradict the theory of endogenous origin. Two routes of exogenous acquisition have been suggested: through ingestion of TTX-rich sediments; or through the symbiotic bacteria that live inside the host organisms. Studies
have demonstrated that puffer fish raised in captivity with TTX-free diet have no or low levels of TTX.

The presence of TTX in bacterial cultures sequestered from such organisms as xanthid crabs, red calcareous alga, puffer fish and others suggest not only bacterial synthesis of the neurotoxin but also symbiotic or commensalistic relationship. Some bacterial genera that produce TTX are: Aeromonas; Alteromonas; Escherichia coli; Otolobacterium phosphoreum; Plesiomonas shigelloides; Pseudomonas sp.; and Vibrio sp..

Conversely evidence of elevated amounts of TTX in tree frogs raised in diet-controlled environment suggests endogenous production of TTX. In newts, Tarichagranulosa, the theory of endogenous TTX-production is supported by three major evidences: lack of bacterial DNA in TTX-rich tissues, secretion of TTX by cells in response to mild electric stimuli, and presence of elevated amounts of TTX in individuals raised in captivity.

**TTX in the Food Chain**

![TTX-producing Marine Bacteria](image)

**Evolutionary History of TTX in Host Organisms**

**Function of TTX**

TTX acts as chemical defense in most organisms. For such predators as puffer fish, TTX resistance (discussed below) allows them to prey upon TTX-laden marine organisms (that is, gastropods, marine worms, starfish), that are toxic to puffer fish’s competitors. Similarly, TTX resistance in garter snakes allows them to feed on toxic newts. In freshwater habitats, tetrodotoxin not only serves as a chemical defense in adult newts but also as a signal of predation risk for newt larvae, that cannibalistic adults prey on. Furthermore, TTX serves as a pheromone in pufferfish, Fuguniphobles, and attracts sexually mature males to the females that secrete the toxin.

Contrary to the idea that presence of TTX in prey would avert the predators, some carnivorous snails are triggered to consume TTX-containing prey. TTX-producing salivary glands of the blue-ringed octopus may be used for paralyzing prey. A bite from the blue-ringed octopus is more fatal than ingestion of puffer fish because the injected TTX can reach the neurons more quickly than ingested TTX.

**TTX resistance in host organisms**

TTX resistance in puffer fish and newts is the result of a single amino acid mutation in the voltage-gated sodium channel, which replaces aromatic amino acid (tyrosine or phenylalanine).

**TTX resistance in predators and subsequent fitness tradeoffs**

Garter snakes, predators of the newts Tarichagranulosa, have developed resistance to TTX due to several amino acid substitutions in the voltage-gated sodium channel. Furthermore, a range of TTX resistance is observed in populations of garter snakes corresponding to the levels of amino acid substitution. Although this evolutionary arms race has enabled garter snakes to prey upon on the highly toxic newts, it might have a downside. Researchers hypothesize reduced speed in garter snakes as a result of this alteration in the voltage-gated sodium channel. This may make them a more vulnerable prey item.

**TTX in Human Use**

Recent TTX poisoning by various organisms has happened in Indo-Pacific ocean regions and in the Atlantic Ocean, the Gulf of Mexico and the Gulf of California as well.

**Human consumption of puffer fish**

**Preparing fugu fish as a delicacy**

In Japan, trained and licensed chefs prepare fugu fish (puffer fish) as a delicacy—some may leave a trace of TTX in the fish for customers to experience lip and tongue tingling without the risk of paralysis. Preparation method determines the high price of fugu fish. One way to eat puffer fish is to slice it thinly, almost transparent, and eat it as sashimi; people also dip fugu fish slices into Japanese soup; salted and grilled fins also serve as appetizers.

**Haitian Voodooism**

Haitians believe that bokors (leaders of Vodou) can create zombies by cursing and casting magic powder at a person. Tetrodotoxin is an ingredient of the powder that causes paralysis of victim making them appear dead, but actually the victim is still conscious. After the family buries the victim, bokors will open the grave and release the undead victim. The victim and other people will think him a zombie that has come back to life.

**Medicine usage**

Because taking TTX blocks voltage-gated sodium channel and causes paralysis, it can also work as a potential pain relief. Long-term treatment of TTX is tolerable to reduce cancer pain. Pain relief can last for weeks with a 4-day treatment cycle, but the mechanism of this phenomenon is unclear. Tetrodotoxin is listed as Department of Health and Human Services (HHS) Select Agents and Toxins. Therefore, scientists need to register with HHS for investigations that use more than 100mg TTX.

This article was researched and written by students at Mount Holyoke College participating in the Encyclopedia of Earth’s (EoE) Student Science Communication Project. All articles have been reviewed and approved by EOE editors, and in many cases individual experts in the appropriate fields.

**Footnote**


**References**


- All about fugu. How to Cook Fish.
- Pufferfish. National Geographic.
- Tetrodotoxin (Captain James Cook). Chemistry Blog.
- Tetrodotoxin. Toxipedia.
- Toxin Registration. UC Davis Safety Services.


Citation


The Authors

Prakriti Kaini is a senior at Mount Holyoke College pursuing a Biology major and Chemistry minor. Her academic interests include larval ecology, animal behavior, and environmental chemistry. She has worked with Prof. Renae Brodie for the past three summers studying the impact of salinity on the osmoregulation and geographical distribution of fiddler crabs. Her future interests lie in working with a non-profit organization in Nepal that addresses the issue of environmental contamination and toxification (Full Bio).

Ivy Li is pursuing her bachelor's degree in environmental studies from Mount Holyoke College specializing in conservation. She spent her previous summer studying landscape architecture at Harvard Career Discovery, followed by working as a bilingual editor at Turenscape Landscape China magazine in Beijing. Last year, she was studying abroad in Madrid, Spain. This past summer as an environmental journalist at chinadialogue, she published online articles on international environme (Full Bio).

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