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Tetrodotoxin : A Threat And A Therapy

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Abstract:

Tetrodotoxin (TTX) is a potent neurotoxin initially discovered in pufferfish and various other marine species. It is produced by bacteria and acts by blocking voltage-dependent sodium channels, leading to paralysis and, in severe cases, death. TTX has therapeutic potential in treating cancer-related pain, neuropathic pain, and even withdrawal symptoms from heroin and cocaine. The toxin has shown efficacy in preventing brain damage following strokes or cardiac arrests and has been studied as a potential anesthetic. Additionally, TTX displays promising results as a tumor suppressor. Among challenges such as toxicity and resistance, research indicates TTX may serve various medical purposes, offering hope for a range of conditions. Further exploration into the clinical application of TTX is warranted based on the emerging positive findings.

Keywords: Tetrodotoxin, TTX, neuropathic pain, anesthesia, Sodium channels, addiction

Introduction:

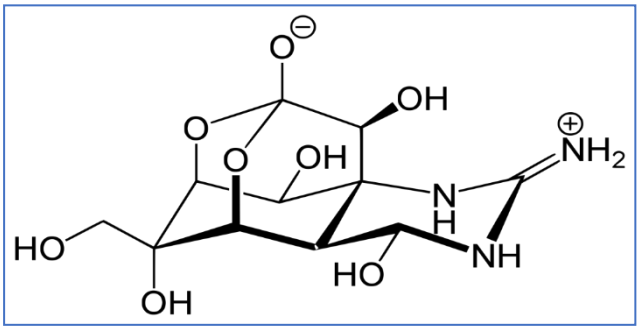
Tetrodotoxin (TTX) is an extremely potent neurotoxin. Its name comes from the order Tetraodontiformes, which includes pufferfish, porcupinefish, ocean sunfish, and triggerfish; several of these species carry the toxin. Although tetrodotoxin was discovered in these fish, it can also be found in a variety of other animals. It is also produced by infectious or symbiotic bacteria such as Pseudoalteromonas, Pseudomonas, and Vibrio, as well as other species that coexist with animals and plants. Skeletal muscle paralysis and death are caused by the highly selective and powerful blocker of voltage-dependent sodium channels in motor nerves by tetrodotoxin. It also blocks some voltage-sensitive sodium channels in sensory nerves, which are important for nociception. TTX is a colorless, crystalline, weakly basic substance with the molecular formula of $C_{11}H_{17}O_8N_3$.

There have been at least 30 structural analogues described so far, with varying degrees of toxicity. These are classified into three groups based on their structure: hemilactal, lactone, and 4, 9-anhydro types, collectively known as tetrodotoxins (TTXs). TTX is both water soluble and heat stable, so heat processing does not destroy it; instead, it increases its toxic effect, and there is currently no known antidote for TTX. Despite its known poisonous, or sometimes lethal, effects when ingested by humans at high doses, TTX has therapeutic properties when administered at much lower levels, which have so far been primarily used to treat cancer-related, neuropathic, and/or visceral pain. Furthermore, TTX has the potential to treat a wide range of medical conditions, including heroin and cocaine withdrawal symptoms, spinal cord injuries, brain trauma, and certain types of tumors.

Structure, Resistance & Toxicity Potential:

TTX's toxicity mechanism has been studied in various animal models. TTX works by blocking sodium channels, which reduces the membrane excitability of vital tissues such as heart myocytes, skeletal muscles, and the central and peripheral nervous systems, resulting in typical symptoms and, in severe cases, death. In mice, its LD50 values range from 10 µg/kg (intraperitoneal), 16 µg/kg (subcutaneous), and 332 µg/kg (oral), indicating that it is unquestionably toxic to mammals. In humans, lethal doses of TTX range from 1.5 to 2.0 mg, or 9 ng/mL of blood. It is approximately 1000 times toxic to humans than cyanide poison. The majority of cases of TTX intoxication and fugu-related fatalities occur in Japan, China, and Taiwan, where pufferfish are traditionally consumed and considered a delicacy. While there were about 100 deaths per year in Japan in the early twentieth century, more recent data indicate that there are about 40-50 intoxication cases per year, with about 10% of these resulting in death.

Figure: Molecular Structure of Tetrodotoxin



The possibility that organisms carrying TTX are immune to the toxic effects of TTX has piqued the interest of numerous researchers. The reason is that these animals' sodium channels cannot be blocked because a non-aromatic amino acid chain replaces the aromatic one in the p-loop region of domain I that contains sodium channels.

Therapeutic Importance:

One of the most promising applications of TTX therapy is in the treatment of general cancer-related pain. Cancer pain is one of the few areas in which the effects of TTX as an

analgesic have been studied in both animal models and people. Pre-clinical and clinical research evaluating the efficacy of TTX injections in the treatment of mild to severe cancer pain show promise for TTX's future usage in the clinic. A study on rats found that local injections of TTX reduced neuropathic pain caused by the colorectal chemotherapeutic drug Oxaliplatin TTX was given at increasing levels (0.03-1.0 µg/20 µL) every 45 minutes for 4 or 15 days after Oxaliplatin injection. At 4 days, rats administered 0.1 µg of TTX or greater showed a substantial rise in nociceptive mechanical threshold, with the highest effectiveness reported at 1.0 µg. After 15 days, the 1.0 µg dose showed a substantial rise in mechanical nociceptive threshold, lowering chemotherapy-induced neuropathic pain. Additionally, TTX in doses of 1.0, 3.0, and 6.0 µg/kg has been proven to suppress neuropathic pain induced by a different chemotherapeutic drug, Paclitaxel, with no symptoms of toxicity or harmful side effects.

Neuropathic pain is caused by a disease or injury to the somatosensory system, which causes it to function abnormally. One distinguishing feature of neuropathic pain is a spontaneous painful sensation caused by ectopic action potentials in nociceptive pathways. TTX has been extensively studied for its ability to treat neuropathic pain, and it has been shown to be effective in several rodent models. Throughout these studies, no motor in-coordination, motor deficiencies, respiratory distress, or sedation were observed. TTX is of particular interest for use as a neuropathic pain treatment because it does not produce any of the deleterious side effects typical of opioid use, such as addiction, inflammation, sedation, and respiratory depression. It also has value in treating visceral pain and chronic pain by targeting $NaV_{1.1}$ channels.

Patients who have experienced a stroke or cardiac arrest may benefit greatly from TTX as a preventative and therapeutic treatment for brain damage. For instance, by decreasing axonal and terminal sprouting, which can result in excitatory connections that cause the brain's circuits to become hyperexcitable, TTX treatment following a traumatic brain injury seems to prevent the onset of post-traumatic epilepsy. TTX may improve pruning by inhibiting neuronal activity in the damaged cortex, though the exact mechanisms are unclear. In two different rat models, TTX was also shown to prevent irreversible cell and tissue damage caused by hypoxia and ischemia. In a separate study with rats, TTX was found to delay anoxic depolarization, the uncontrollable depolarization of neurons during brain ischemia, and the resulting neuronal death. In these cases, the effect appears to be due to the prevention of membrane depolarization, which inhibits the activation of voltage-gated calcium channels and the release of calcium from intracellular

stores, thus avoiding the cytotoxic effects of high intracellular calcium concentrations.

Researchers have also looked into the efficacy of TTX as an anesthetic. Early studies on the topical application of TTX to rabbit cornea revealed that the toxin produced a long-lasting anesthetic effect (up to 8 hours) with no signs of systemic toxicity, ocular irritation, or corneal thickening, even when applied repeatedly over a 24-hour period; TTX also did not inhibit epithelial healing in the affected cornea. Beyond topical anesthesia, TTX has proven to be an effective local anesthetic, particularly when combined with epinephrine or bupivacaine. A toxic dose of TTX is required to produce a sciatic nerve block; however, when combined with 1.1 μM epinephrine, TTX can be used at lower concentrations and the duration of blocks increased by tenfold. With a limited margin of safety, the combination of TTX, bupivacaine, and the anti-inflammatory drug dexamethasone resulted in long-lasting nociceptive blocks. In contrast to bupivacaine and bupivacaine-epinephrine combinations, the duration of the nerve block was roughly tripled when TTX, bupivacaine, and epinephrine were combined.

The potential effectiveness of TTX as a tumor suppressor is shown by a number of encouraging studies. In a non-small cell lung carcinoma cell line (H460), TTX was found to 50% decrease cell invasion without affecting non-invasive wild-type cells. While TTX had no effect on metastasis or proliferation, it did reduce the invasive capacity of cervical cancer cells by 20%. When two ovarian cancer cell lines, Caov-3 and SKOV-3, were treated with a very high dose of TTX (30 μM), migration and invasion were greatly decreased, but not proliferation.

One of the biggest obstacles to effectively treating heroin addiction is the recurrence of heroin withdrawal symptoms. Recovering addicts may resume drug use even after extended periods of abstinence due to stressors or environmental cues linked to drugs. A single intramuscular injection of 10 μg TTX significantly decreased cue-induced anxiety and craving in abstinent recovering heroin addicts in a 2009 double-blind, placebo-controlled study with 45 participants. Blood pressure and heart rate were not significantly affected. In a different double-blind, placebo-controlled study with 216 participants, intramuscular injections of 5 or 10 μg TTX three times a day significantly decreased withdrawal symptoms in newly abstinent addicts by the third day of the trial without having any negative effects on blood pressure or respiration. According to these two studies, TTX may be useful in reducing opiate withdrawal symptoms and averting relapse. Additionally, experimental evidence indicates that TTX is not addictive, and established effective dosages do not present a risk to the heart or neurons, making it a potentially appealing substitute for opioid treatments. A possible mechanism of this may

be due to its effects on basolateral amygdala and the nucleus accumbens.

Conclusion:

Tetrodotoxin is a very lethal zootoxin produced by various animals of different taxa. It has been a well-known cause of human death in many South-East Asian countries due to consumption of marine species of animals containing TTX. The production of these toxins in these species of animals is mostly attributed to the symbiotic bacteria present in these animal species. In recent years the therapeutic potential of this toxin is studied in animal models and also tested in humans. TTX has shown promising results in therapy of cancer related, chronic and visceral pain. Additionally, it also has been used in treatment of drug addiction, tumors, CNS injuries and is also tried as an anesthetic agent.

References:

Bucciarelli GM, Lechner M, Fontes A, Kats LB, Eisthen HL, Shaffer HB. From Poison to Promise: The Evolution of Tetrodotoxin and Its Potential as a Therapeutic. *Toxins*. 2021; 13(8):517.

González-Cano, R., Ruiz-Cantero, M. C., Santos-Caballero, M., Gómez-Navas, C., Tejada, M. Á., & Nieto, F. R. (2021). Tetrodotoxin, a potential drug for neuropathic and cancer pain relief?. *Toxins*, *13*(7), 483.

Lago, J., Rodríguez, L. P., Blanco, L., Vieites, J. M., & Cabado, A. G. (2015). Tetrodotoxin, an extremely potent marine neurotoxin: Distribution, toxicity, origin and therapeutical uses. *Marine drugs*, *13*(10), 6384-6406.

Lago J, Rodríguez LP, Blanco L, Vieites JM, Cabado AG. Tetrodotoxin, an Extremely Potent Marine Neurotoxin: Distribution, Toxicity, Origin and Therapeutical Uses. Mar Drugs. 2015 Oct 19;13(10):6384-406

Bane V, Lehane M, Dikshit M, O'Riordan A, Furey A. Tetrodotoxin: Chemistry, Toxicity, Source, Distribution and Detection. *Toxins*. 2014; 6(2):693-755

Nieto, F. R., Cobos, E. J., Tejada, M. Á., Sánchez-Fernández, C., González-Cano, R., & Cendán, C. M. (2012). Tetrodotoxin (TTX) as a therapeutic agent for pain. *Marine drugs*, *10*(2), 281-305.

https://en.wikipedia.org/wiki/Tetrodotoxin

https://www.sciencedirect.com/topics/neuroscience/tetrodotoxin

Katikou P, Gokbulut C, Kosker AR, Campàs M, Ozogul F. An Updated Review of Tetrodotoxin and Its Peculiarities. *Marine Drugs*. 2022; 20(1):47.