The progress of the applications of sodium channel blockers

Boxiu Deng[1, a, *, †], Yige Yan[2, b, *, †]

[1]Cangzhou No.1 middle school, Cangzhou, China

[2]Queen elite academy, Toronto, Canada

[a]Dbx20040219@icloud.com, [b]yanyige2018@gmail.com

[†]These authors contributed equally.

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Abstract: Sodium channel receptor poisons are a type of neurotoxin that acts on different locations of sodium channels and thus have distinct toxicological effects. Ingestion of these poisons, such as STX, NSTX, TTX, etc., can cause a strong poisoning reaction in the body, and even death. However, recent studies have shown that these neurotoxins can be used to treat pain, such as neuralgia, headaches, based on the characteristics of sodium channels being inhibited by sodium channel blockers. Moreover, a large number of studies have shown that these neurotoxins also have a certain effect on the treatment of cancer. This study investigated the relationship between different sodium channel blockers, including the differences and applications of different sodium channel blockers. This article will focus on the analysis of the three main toxins, The clinical and industrial use of saxitoxin (STX), neurotoxin (NSTX), and tetrodotoxin (TTX) and Introduction to clinical and biological trials of TTX (Tetrodotoxin), and the application of these three toxins in clinical, industrial, and pharmaceutical aspects.

1. Introduction

Sodium channel is an important part of our neuron system. A small but considerable amount of Na + ions will flow into the cell along their electrochemical gradient if enough channels open when the cell's membrane potential changes, further depolarizing the cell. And it also has Impermeability to other ions. Sodium channel toxins have lately gained more attention in the literature. Some sodium channel blockers are indeed becoming more readily available for mass manufacturing than they were previously. The sodium channel blockers will influence the sodium channel in medicine that allow us to deal with some diseases. They are divided into two main species, intracellular sodium channel blockers, and extracellular sodium channel blockers. Just like their name, Intracellular sodium channel blockers are drugs that inhibit sodium channels by blocking them from the intracellular side such as lidocaine, Class I antiarrhythmic agents, and Various anticonvulsants: phenytoin, oxcarbazepine (derivative of carbamazepine). The extracellular sodium channel blockers are the naturally occurring chemicals that obstruct sodium channels by binding to and occluding the channel's extracellular pore opening. Sodium channels blockers decrease cell excitability and conduction velocity by slowing the rate and magnitude of early rapid depolarization. Ectopy is suppressed by several sodium channel blockers, notably slowly dissociating sodium channel blockers, often known as "class Ic medicines" in the previous Vaughan-Williams classification [1]. The induction of refractoriness beyond the end of the action potential is a significant, and sometimes underappreciated, impact of such compounds. This post repolarization refractoriness seems to decrease inducible ventricular fibrillation, and it's a well-known impact of sodium channel blockers like propafenone or flecainide4, as well as amiodarone and dronedarone.

The main purpose of this paper is to discuss the application of three different kinds of extracellular sodium channel blockers toxins which are saxitoxin (STX), neurotoxin (NSTX), and tetrodotoxin (TTX), focusing on their definitions, mechanism, and some medical applications. They play a

significant role in various neurological diseases, including antiarrhythmic medicine, analgesic, anticonvulsants, and depression, which affect action potential.

2. Saxition

STX is a very powerful neurotoxin and the most toxic paralytic shellfish toxin known. STX is actually synthesized by some algae under the phylum dinoflagellate, such as Alexandrium, Gymnodinium, and cyanobacteria in freshwater such as Anabaena, which accumulate in the shellfish through the food chain. Due to its extreme toxicity, STX is classified as Agent TZ (chemical weapon designation) and is believed to have chemical weapon potential. Researchers have demonstrated that saxitoxin-laced bullets may be used to ensure the victim's quick death. STX is far more deadly than the synthetic nerve gas sarin, and it is classed as a biological weapon, along with the phytotoxin ricin. The Chemical Weapons Convention lists STX. The poison is also listed in the German War Weapons Control Act's Annex (War Weapons List). After these algae are eaten by the shellfish, the toxins produced are accumulated in the shellfish's filter organs. Toxins produced by different toxic algae have distinct types and contents, and toxins produced by the same toxic algae have different types and contents at different phases of growth. STX is a neurotoxin that operates as a voltage-gated sodium channel blocker that is selective and reversible. It is one of the most powerful natural poisons known, acting on neurons' voltage-gated sodium channels, inhibiting normal cellular activity and resulting in paralysis.

At the same time, biological and non-biological factors have an impact on toxin generation. Toxins can also be passed on to larger predators. Organisms enhance the aquatic food chain, which is then passed on to terrestrial biota, and lastly to people. STX interrupts neurotransmission by binding to voltage-gated sodium channels. The positively charged guanidine group of STX interacts with the negatively charged carboxyl group at a site on the sodium channel of neurons and muscle cells in a one-to-one ratio, causing the action potential to be blocked and transmission interrupted. This is followed by inactivation of vasomotor nerves and relaxation of vascular smooth muscles, and hypotension may also occur.

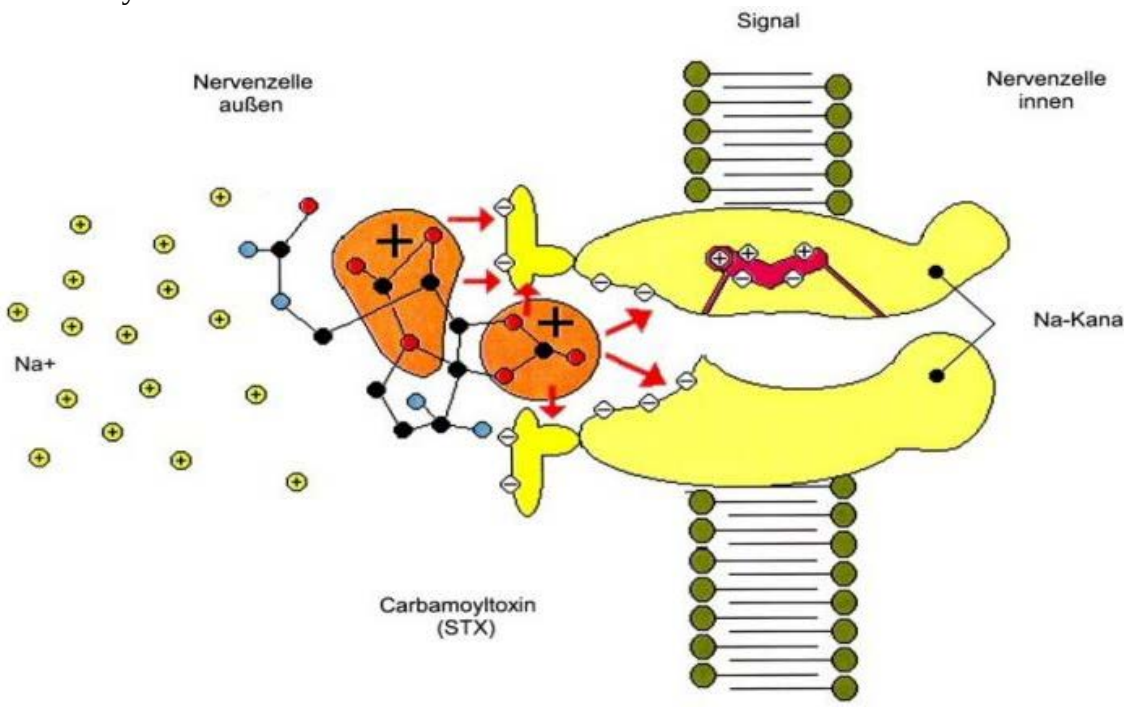

Figure 1. Model of how PSP toxins bind to the surface of excitable nerve cell membranes [1].

STX binds to voltage-gated sodium channels on neurons. The positively charged guanidine groups of STX interact with the negatively charged carboxyl groups on the sodium channels of neurons in a one-to-one ratio, affecting action potentials and inhibiting normal cell activities.

Humans are often poisoned by accidental consumption of STX-containing shellfish and other seafood. The symptoms of poisoning are often different depending on the amount of ingestion. Mild poisoning is manifested as nausea, vomiting, diarrhea, and local skin numbness or tingling. After severe poisoning, it manifests as neuromuscular paralysis, voluntary muscle weakness, respiratory muscle contraction weakness, blood pressure drops, heart rate slows down, and arrhythmia. Patients often feel a sense of floating in the body, and they can die within 15 minutes of severe poisoning. STX poisoning has a significant death rate, and there is no specific antidote; instead, symptomatic and supportive care is used. On the basis of traditional treatment, the following two measures were mostly used in this case of poisoning to maintain the body's mildly alkaline internal environment. According to the results of the blood gas test, an intravenous infusion of 5% sodium bicarbonate solution was administered to keep the blood gas pH between 7.40 and 7.45., HCO3-24 27mmol/L until the patient had superficial spontaneous breathing movement. Exchange blood treatment is another option. It can quickly reduce the blood toxin concentration, promote the body's metabolism and detoxify at the same time, which is relatively safe [2].

In the study of smooth muscle and myocardial ion currents, nanochannel structure, and the influence of chemical drugs on neuromuscular conduction, it has become an important tool for the study of nanochannels. The most important thing is that STX has significant antitumor and antiviral activities, and is highly destructive to cancer cells. It is very likely to be an important material for the development of anti-cancer drugs in the future. STX lowers the eel's peripheral blood pressure by causing cardiovascular catheterization. The reduction in cardiac contractility is accompanied by this impact. STX blocks the heart's conduction system, and the degree of blockage is generally related to the STX dose. The effects of STX on heart rate are only temporary. Although epinephrine (0.3g kg-1) cannot reverse STX's antihypertensive impact, it helps hasten blood pressure recovery [3].

STX has long been employed in military laboratories, in addition to medical. It is considered to be incomparable to the nerve agent used in large-scale distribution, although it is more beneficial as poison bomb equipment. It's used to shoot STX into the human body with a gun, and it merely feels like a mosquito bite, but it will cause death in less than 15 minutes, considerably faster than bacterial toxins [4]. Overall, STX as a synthetic neurotoxin has played a significant role in our understanding of poisons, whether they are utilized to help or harm people. And under many monitoring methods, STX has rarely caused direct harm to people. This is not only a further step in safety but also means that this toxin has been better understood by us.

3. Neo saxitoxin

Neo saxitoxin (NSTX), along with other saxitoxin-analogs, is part of a large group of naturally occurring neurotoxic alkaloids known as the paralytic shellfish toxins (PSTs). Paralytic shellfish poisoning is carried by the toxins-containing bivalve shellfish (such as mussels, oysters, and clams) whose poisons have the potential to have serious and life-threatening neurological consequences like dizziness, drowsiness, diplopia, nausea, and vomiting [5]. The main difference between NSTX and STX, as well as all other neurotoxins linked to PSP, is that NSTX has one hydroxyl group attached to nitrogen "1," whereas STX has one hydrogen. Cooking does not degrade this purine since it is extremely hydrophilic and thermostable [6]. Furthermore, it is quite stable under normal storage, particularly in acidic conditions. These poisons NSTX inhibit the extracellular part of certain voltage-gated sodium channels, the outer vestibule, in a highly strong and reversible way, without affecting other ion channels. In this condition, it is possible that we will be able to find an antidote to NSTX by studying its characteristics.

"Voltage-gated," "voltage-sensitive," and "voltage-dependent" sodium channels, commonly known as "VGSCs" or "Nav channel," are essential components of proper physiology in a wide range of species, including flies, leeches, squid, and jellyfish, as well as mammalian and non-mammalian vertebrates [7]. In neurons, myocytes, and other excitable cells, this large integral membrane protein is required for the initiation and propagation of action potentials. The ability that blockers the sodium channel of the NSTX determines the role it will play in medicine [8]. Researchers used 10 healthy

participants in a randomized, double-blind, placebo-controlled study. Subcutaneous injections of 50 microg NSTX were given in the middle posterior skin of the calf, whereas the contra-lateral leg got a placebo. A validated human sensory and pain model was used to assess the anesthetic effect. The result is cheerful that the assessed parameters were effectively and completely blocked for all of the patients. Heat discomfort was the first to return to normal values after 3 hours when the blockage began to reverse. Cold pain was the feeling that was blocked the longest, lasting 24 hours. In blood and urine tests, the poison was undetectable. There were no neo saxitoxin-related side effects discovered. As a result of the foregoing tests, NSTX appears to be completely capable of being used in neuralgia.

But NSTX still has dangerous to use on medicine, especially use on children. When progressive supranuclear palsy (PSP) epidemics occur in rural areas with inadequate medical resources, documented mortality in adults is less than 10%, but it can approach 50% in children under the age of six. This disparity might be due to different dosages and compositions of the PST mixes involved, a delay in medical assistance, or some type of sensitivity in youngsters [9]. Because of this, although the clinical experiment shows the possibility to use on Local Anesthetic, there are some potential risks to use Neosaxintoxin. Surprisingly, chronic and/or recurrent exposure to marine seafood toxins, a far more common occurrence, has not been well investigated. In one research, rats were given prolonged (12-week) NSTX showed a decrease in water and food intake, as well as a modest form of transitory cholestasis, most likely due to fasting, but no other abnormalities. And there are already two more efficient and safe toxins that are full of studies and clinical experiments that play a role in this area, so the application of NSTX is relatively scarce.

4. Tetrodotoxin

Tetrodotoxin (TTX) is a neurotoxin that may be found in both land and sea species, including dolphins. TTX is a neurotoxin with high potency. Pufferfish, porcupinefish, ocean sunfish, and triggerfish are all members of the Tetraodontiformes order, and numerous of these species contain the toxin. TTX is generated by some infecting or symbiotic bacteria such Pseudoalteromonas, Pseudomonas, and Vibrio, as well as other species found in animals, such as blue-ringed octopus, rough-skinned newts, and moon snails. It's been utilized to figure out what role it plays in voltage-dependent sodium channel subtypes (VGSCs). In a variety of physiological and pathological processes of the central nervous system, VGSC plays a vital role in pain [10]. The sensitive subtype of TTX has received a lot of attention in recent years. Because these pathways are linked to both normal and pathological pain, and because TTX is extremely selective in inhibiting this section of VGSC, the medication might help with pain reduction. Many researchers have utilized TTX to characterize the function of VGSC in normal physiology and illness, as well as the molecular mechanisms underlying pain. Its involvement has been investigated in different pain animal models, as well as pain relief studies in clinical settings.

Marcil and his colleagues used a rat formalin model to evaluate TTX. The first score of acute formalin discomfort in rats was decreased by systemic injection of TTX (highest dosage), but the change was not significant. The researchers discovered that systemic TTX had no influence on the responsiveness of control rats to heat stimulation in another investigation. The researchers also discovered that systemic TTX had no impact on nociceptive mechanical pain, but mexiletine elicited a strong antinociceptive response and increased leg pull-out latency [10]. Finally, intrathecal injection of TTX reduced intact rats' heat sensitivity, and its inhibitory titer was roughly 300 times that of carbamazepine, according to a recent study. Carbamazepine is thought to have an inhibitory impact on TTX sensitive and TTX resistant sodium channels, implying that TTX may have a minimal therapeutic effect on acute pain. However, further study is needed to elucidate this issue using various delivery methods.

TTX has been studied in a model of neurogenic pain caused by chemotherapy, with mixed results [11]. In rats, systemic treatment of TTX has been shown to not affect the expression of mechanical hypersensitivity to vincristine-induced pain. TTX inhibits the expression of paclitaxel-induced

mechanical, cold, and thermal hyperalgesia in mice, according to the study. TTX has also been shown to fully avoid two allergic responses, according to the researchers. Different research might be related to the antitumor actions of paclitaxel and vincristine, both of which can cause clinically severe peripheral neuropathy, and the harmful mechanism is unknown.

Furthermore, TTX has been shown to reduce capsaicin-induced mechanical hypersensitivity in mice, a model of neurogenic pain that is considered an alternative [12]. DRG perfusion at the location of TTX damage reduced astrocyte activation following peripheral nerve injury, increased NGF expression in DRG, and activated microglia and astrocytes in the spinal cord, according to the findings. Only one research found that an adequate dosage of TTX did not prevent neuropathic pain in mice. As a result, many data support the hypothesis that TTX has a function in the treatment of neuropathic pain and that TTX sensitive VGSC plays a crucial part in the neuropathic pain state. They contrast sharply with the results of VGSC knockout mice, however, the emergence of compensating mechanisms in these animals cannot be overlooked when compared to TTX-treated mice. More study is needed to fully understand this issue [13].

TTX's analgesic impact has been studied in a number of clinical studies. In an open-label multicenter trial, 24 patients were given one of 31 treatment regimens, which included injectable TTX at a dosage of 15-90 g/d. Of the 31 treatment regimens, 17 substantially decreased pain intensity, with pain relief lasting up to two weeks [14]. The result shows that 30 g twice a day for four days was a safe and effective analgesic regimen. Subcutaneous TTX had no clinically significant pain relief in cancer patients with moderate to severe pain when only pain scores were evaluated in a double-blind, placebo-controlled, parallel design study. However, further analysis of the data revealed a strong analgesic effect, and all patients could participate in an open multicenter study to expand the efficacy and safety. TTX has been tested in a model of chemotherapy-induced neurogenic pain, with inconsistent results [15]. The expression of mechanical hypersensitivity to vincristine-induced pain was not affected by systemic TTX administration in rats. According to the study, TTX suppresses the expression of paclitaxel-induced mechanical, cold, and thermal hyperalgesia in mice [16]. To summarise, TTX is a helpful sodium channel toxin that blocks pain on the nerves and may be used to assist individuals to endure pain in a variety of situations. As mentioned earlier, STX, NSTX, and TTX have all been proven effective in clinical trials, and studies have shown that they are great hopes for the treatment of neuropathic pain patients [17].

5. Conclusion

In conclusion, because all three poisons are fatally paralyzing and no antidote has been discovered, they are extremely hazardous. However, as a result of their inhibition of cell activities, they do exceptionally well in clinical medicine. STX has significant antitumor and antiviral activities that are highly destructive to cancer cells and can effectively reduce blood pressure. It is an important tool for nanochannel research, and it has also played a great role in military research. As a synthetic nerve poison, it plays an important role in our understanding of poisons. The toxin TTX has been studied as a potential therapy for cancer-related discomfort. Early clinical trials show that some individuals get considerable pain alleviation. In addition to the cancer pain application, mutations in one specific TTX-sensitive Na+ channel have been linked to certain migraine headaches; however, it is unclear if this has any therapeutic implications for the majority of migraine sufferers. The scientists can explore more about TTX, like use it on the operation or other neuropathic diseases. NSTX is relatively more dangerous to children and there are only a few studies about it. But NSTX also shows a potential to use medicine to block the pain, in the future, we can focus on the application of NSTX to find other useful toxins on the neuropathic pain which is safe, helpful, and no side-effect. These three toxins have great potential in the treatment of neuropathic pain. Other Sodium channel blockers are also utilized as anticonvulsants and local anesthetics. The use of sodium channel blockers in the treatment of cystic fibrosis has been advocated, however current data is equivocal. Some antidepressants' analgesic effects have been proposed to be mediated in part by sodium channel blockage.

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