Marine Neurotoxins: a Double-edged Sword in Food Industry and Brain Research

Liying Huang[1], Likun Gong[2], Xiang Xue[3*], Yuexing Zhang[4*]

[1] Marine Fisheries Research Institute of Zhejiang, Marine and Fishery Institute of Zhejiang Ocean University, Zhoushan 316021, China;

[2] Center for Drug Safety Evaluation and Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China;

[3] Department of Molecular and Integrative Physiology, University of Michigan Medical School, Ann Arbor, Michigan, USA;

[4] Marine Science and Technology College of Zhejiang Ocean University, National Engineering Research Center For Marine Aquaculture, Zhoushan 316022, China.

Corresponding to: Xiang Xue, Ph.D., Department of Molecular and Integrative Physiology, University of Michigan Medical School, Ann Arbor, Michigan, 48109, USA. Email:xxue@umich.edu;

also Corresponding to: Yuexing Zhang, Marine Science and Technology College of Zhejiang Ocean University, National Engineering Research Center For Marine Aquaculture, Zhoushan 316022, China. Email: yuexing.zhang@zjou.edu.cn.

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ABSTRACT

Marine organisms are important food resource for human. Diversified neurotoxins have been found in marine organisms. In order to effect effectively in ocean, marine neurotoxins are often multiplied potent than other toxins. Therefore the safety of marine products is critical for human health. Here we summarize the current potent marine neurotoxins and their derivatives based on their latest application in neuron science research. Their toxicity mechanism is also discussed. Most of the toxins specifically act on ion channels including Na^+, K^+, Ca^{2+} channels, a few interact with receptors like glutamate receptor or nicotinic acetylcholine receptors thus can have effect on neurons. They are frequently used as agonist or antagonist either blockade the channel or excite the potential. Overall, it is worthwhile to make use of this double-edged sword pharmacologically and scientifically.

Keywords: marine toxin, neurotoxicity, voltage-gated ion channels, sea food safety

1 INTRODUCTION

Marine animals have unique way to defense because of their soft body, relatively immobile and lack of obvious physical strength. Living in an enormous and diverse space provided by the ocean, they may accumulate and use a variety of toxins for their protective purposes. The toxins vary from small molecules to peptides, and display unique chemical and biological features of scientific interest. Due to environmental change and pollutions, possibly for the purpose of surviving, there are more neurotoxins released by marine organisms [1]. The released neurotoxins are harmful for human and animals that eat them. There are reports that seafood has been recalled due to toxins that cause brain damage. Thus it is important to detect the presence of neurotoxins in marine food industry [2]. On the contrary, the potent neurotoxicity can serve as useful research tools, the substance's unique structure can also serve as molecular models for the design of new drugs and pesticides [3]. This paper summarizes some of the new advances in known neurotoxins and specifically their application in neuron science research.

Marine neurotoxins cause neurotoxicity mainly by interacting with voltage-gated Na^+, K^+ and Ca^{2+} channels and modulating the flux of these ions into cells, resulting in adversely affected functions in both developing and mature nervous tissue [4, 5]. Because marine neurotoxins specifically target neural components, it is important to use them in the research of animal model for brain disorders [6]. Pseudomonas aeruginin as representation of polyetropoid toxins produced by dinoflagellates, is a voltage-dependent Na^+ channel agonist that increases the permeability of Na^+ to the cell membrane, resulting in strong depolarization, causing neuromuscular excitability change. While the others are produced by marine bacteria and actinomycetes toxin, like tetrodotoxin is Na^+ channel blockers, binding to the outside of Na^+ channel, thus blocking the passage of Na^+. Some bacteria and algae produced by the stone nectar is also Na^+ channel blockers, causing neuromuscular signal transmission failure, leading to paralytic poisoning. In addition, some of the peptides produced by blue bacteria can also make Na^+ channel inactivation, which cause strong neurotoxin. K^+ channel inhibitors are also an important group of natural products found in marine neurotoxins. There are other neurotoxins acting on the Ca^{2+} channel, with both effects of block and excitement. Moreover, some compounds or peptides can bind receptors like glutamate receptor or Nicotinic acetylcholine receptors thus can have effect on neurons.

Table 1. Summary of the marine neurotoxins

Neurotoxin	Molecular target	Organisms	Application
Tetrodotoxin (TTX)	Na+ channel	Puffer fish	1. Selectively inhibit Na+ 2. Analgesic
Ciguatoxin (CTX)	Na+ channel	Gambierdiscus toxicus	1. Agonist of voltage-dependent Na+ channels
Azaspiracid-1 (AZA-1)	Na+ channel	Algae	1. Inhibit the activity of Na+ channels with glutaric acid 2. hERG channel blocker
Sea anemone toxin	Na+ channel, K+ channel	Sea anemones	1. ATX-2, Calitoxin and anthopleurin selectively act on the Na+ channels 2. BDS-I/II specifically inhibit Kv3-family K+ channels 3. Kaliseptine and kalicludines selectively blockade K+ channels

Conotoxin (CTX)	Na+ channel, Ca2+ channel, AchR	Cone snails	1. μ-CTX, δ-CTX specifically suppresses voltage-sensitive Na+ channels 2. ω-CTX selectively blockade Ca2+ channel 3. α-CTX blockades neuronal chondrocyte acetylcholine receptors (AchR) 4. Analgesics 5. Pain relief
Saxitoxin (STX)	Na+ channel, K+ channel, Ca2+ channel	Dinoflagellates	1. Selective Na+ channel blocker 2. Act on K+ and Ca2+ channels
Palytoxin (PLTX)	Na+ channel, K+ channel	Palythoa, Ostreopsis	1. Act on the Na+-K+-ATPase
Domoic acid (DA)	Glutamate receptor	Algae	1. AMPA/kainate receptor agonist
β-N-methylamino-L-alanine (BMAA)	Glutamate receptors	Mollusks	1. Act glutamate receptors
Nereistoxin (NTX)	Nicotinic acetylcholine receptors	Annelid worm	1. Selectively blockade nicotinic receptors 2. Insecticide
Anabaseine	Nicotinic acetylcholine receptors	Nemertines	1. Acetylcholine receptor agonist

2 Classification of marine neurotoxins

According to marine neurotoxins' various toxicity mechanism, we grouped them in this review we group them based on the channels/receptors they interact with. However, some toxins have multiple targets, we addressed them in each category. They are summarized in table 1.

2.1 Marine neurotoxins interacting with Na+ channel

The voltage-gated Na^+ channel is crucial for normal neuronal functioning [7]. The components of the channel are integral membrane proteins scattered along the axon of a neuron and each one has four domains. When a voltage changes or ligand binds in the right way, opening of the voltage-gated Na^+ channel occurs. It is very important that these Na^+ channels are functioning properly, as they are essential for the propagation of the action potential. Without this ability, the nerve cell can not transmit signals and the part of the body that it innervates is disconnected from the nervous system. This may lead to paralysis of the affected part. Many marine neurotoxins can specifically or non-specifically act on Na^+ channel.

Tetrodotoxin (TTX), a specific blocker of a voltage-sensitive Na^+ channel, is isolated from puffer fish and has a high degree of Na^+ passage for excitatory cell membranes such as nerves, muscles, and Pujinye's fibers Specificity [8, 9]. The marine flatworm Planocera multitentaculata is a

known TTX-bearing organism, and is suspected to be a TTX supplier to puffer fish [10]. TTX is an important tool for the identification, isolation, and study of Na^+ channels because of its high selectivity and high affinity for blocking Na^+ channels on the neurohormonal membrane [11-13]. However, it is more interestingly that TTX's mechanism of action differs from terrestrial found toxins. It selectively inhibits Na^+ passage through the neural cell membrane at very low concentrations but allow K^+ to pass through. This property is extremely useful for neurobiology and pharmacological studies. TTX is one of the most peculiar natural products of small molecules found in the nature today, and has great potential in drug development [14]. TTX was originally used to treat neuralgia in patients with leprosy as a strong analgesic with relatively slow and long lasting, but no addiction. It is thousands times more potent than usual anesthetic drugs with local anesthetic effect and has significant antiarrhythmic activity. TTX has seven natural derivatives, they selectively blockade function of the Na^+ channel on cell membrane. However, due to their great toxicity, and lack of pharmacokinetic data, they have not been widely used. Thus derivatives that can have reduce toxicity but preserve the potential blocking effect would be of great significance.

Ciguatoxin (CTX) is derived from the genus Gambierdiscus toxicus and all fish that eat this algae accumulate CTX [15]. CTX toxicity is 100 times stronger than TTX. CTX is a new agonist of voltage-dependent Na^+ channels that binds to the channel receptor site VI and increases the permeability of Na^+ to excite the cell membrane, causing strong depolarization, resulting in changes in neuromuscular excitability, inducing a series of pharmacological and toxicological effects [16-18]. Three types of CTX, Pacific cigarettes, Caribbean ciguatoxin, and Indian ciguatoxin have been found [19].

Azaspiracid-1 (AZA-1) is an algal toxin that accumulates in edible mussels. It can induce diarrhetic shellfish poisoning (DSP)-like disease in humans or neurotoxicological symptoms and death in mice [20]. The toxin is able to inhibit neurological signaling in spinal cord neuronal networks, in young cerebellar granule cell cultures and in primary neocortical neurons. At high concentrations it acts as a human ether-a-go-go related gene (hERG) potassium channel blocker [21]. In the presence of glutaric acid, AZA-1 at nanomolar concentration could inhibit the activity of Na^+ channels in vitro. AZA-1 exposure induces an early differentiation phenotype followed by a later cell death in PC12 cells [22]. The differentiated appearance coincides with down-regulation of a specific peripherin isoform, a neuronal specific intermediate filament protein [22].

Sea anemone is a group of neurotoxins isolated from shoreline anemone Palvthora toxicus, P. vestitus, P. mamillosa, and P caribaeorum [23-25]. One sub family of sea anemone toxins acts on the Na^+ channel while another subfamily acts on the K^+ channel [25]. ATX-2 is one of the anemone toxin, which can selectively act on the Na^+ channels of the cell membrane [26-28]. It is also an effective tool for studying myocardium and nerve membrane excitations. Calitoxin and anthopleurin also belong to the sodium channel toxin family [29]. These neurotoxins bind specifically to the sodium channel, thereby delaying its inactivation during signal transduction, resulting in strong stimulation of mammalian cardiac muscle contraction. Calitoxin 1 has been found in neuromuscular preparations of crustaceans, where it causes massive neurotransmitter release, causing firing of the axons [29].

Conotoxin (CTXs) are small peptides toxins consisting of 10 to 30 amino acid residues [30]. They are the smallest neurotransmitter neurotoxins found so far. They can be classified into α, ω, μ, δ and other subtypes, each subtype can still be subdivided. μ-CTX specifically suppresses voltage-sensitive Na^+ channels in the activation phase [31]. While δ-CTX specifically suppresses voltage-sensitive Na^+ channel in the non-activated phase, extending the duration of action potential [32]. Clinically CTX are used as specific diagnostic reagents. Additionally, CTXs also used as analgesics with a curative but non addictive effect. CTXs are interesting molecules with a diverse human therapeutic activities, such as anti-nociceptive, antiepileptic, cardio- and neuro-protective.

Saxitoxin (STX) is a neurotoxin naturally produced by certain species of marine dinoflagellates and freshwater cyanobacteria [33]. STX is associated with paralytic shellfish poisoning (PSP), together with its derivatives they are often referred to as “PSP toxins” [34]. Among the derivatives GTX-III is the only one exhibits comparable toxicity to that of STX. It acts as a selective Na^+ channel blocker, preventing normal cellular function and leading to paralysis [35]. STX and its derivatives are also known to act on K^+ and Ca^{2+} channels [36].

Palytoxin (PLTX) is a potent non-protein marine compound produced by corals of the genus Palythoa and by dinoflagellates of the genus Ostreopsis [37]. Several PLTX analogues have been identified so far, either from Palythoa or from Ostreopsis [38]. PLTX acts on the Na^+ - K^+ - ATPase (sodium pump), thus allows passive transport of both Na^+ and K^+, resulting in an imbalance of the ion gradient that is essential for most cells. This feature enables PLTX be a powerful tool in neuron research.

2.2 Marine neurotoxins interacting with K^+ channels

Voltage-gated K^+ channels are transmembrane channels specific for K^+ and sensitive to voltage changes in many cells membrane potential [39]. They play a crucial role in repolarizing the membrane after the initiation of an action potential. They are also involved in physiological processes, such as neuronal excitability, muscle contraction, neurotransmitter release. The Kv3 K^+ channels, with features of ultra-rapid gating and high activation threshold, are essential for high-frequency firing in many CNS neurons. More important, the Kv3.4 subunit has been implicated in the major CNS disorders such as Parkinson's and Alzheimer's diseases. Therefore, it is implicated that selectively targeting this subunit might have a therapeutic utilization application.

Sea anemone venom is an important source of bioactive compounds used as tools to study the pharmacology and structure-function of voltage-gated K^+ channel [40]. These neurotoxins can be divided into four different types, according to their structure and mode of action. Sea anemone neurotoxin family includes the antihypertensive and antiviral proteins BDS-I (P11494) and BDS-II (P59084) expressed by Anemonia viridis (previously Anemonia sulcata). BDS-I is used as a specific inhibitor of Kv3-family K^+ channels [41]. Both peptides are known to specifically blockade the Kv3.4 potassium channel, and markedly inhibits current through Kv3.1 and Kv3.2 channels, thus bring about a decrease in blood pressure and possible application in degenerative disorders [42]. Because of the effect on K^+ channels, Sea anemones neurotoxins have been widely used as pharmacological tools. Furthermore, some of the toxins are now useful drugs for the diagnosis and treatment of autoimmune diseases [43]. Kaliseptine and kalicludines isolated from Anemonia viridis is in the K^+ channel toxin family too [44]. Kaliseptine binds to the same receptor site as dendrotoxin and kalicludines, function as an efficient K^+ channel inhibitor.

2.3 Marine neurotoxins interacting with Ca^{2+} channels

Voltage-gated Ca^{2+} channels are heteromeric proteins composed of 5 subunits [45]. These channels mediate Ca^{2+} influx into the cell following membrane depolarization. Two distinct classes of Ca^{2+} channels are generally recognized: the high voltage-activated (HVA) and low voltage-activated (LVA) channels. Each class is characterized by the degree of depolarization required for channel activation, a biophysical property that is largely determined by the α1 subunit. Ca^{2+} channel is widely expressed throughout the body, particularly in excitable and secretory cells, Ca^{2+} is a ubiquitous signaling molecule critical to a wide range of physiologic processes in virtually all cell types, including neurons. Thus Ca^{2+} channels are targets for numerous ligands including marine naturally occurring peptide toxins. Some of these peptide toxins are invaluable tools for studying the structure and function of Ca^{2+} channels and have potential therapeutic applications [46].

Among the super family, ω-CTX specifically blockade neuronal enamel presynaptic voltage-sensitive Ca^{2+} channel [47, 48]. They are found in the venom of piscivorous (fish hunters), vermivorous (worm hunters), and molluscivorous (mollusk hunters) cone snails. The most extensively analyzed ω-conotoxin to date is ω-MVIIA, which blockades CaV2.2 ion channels. This conotoxin has been approved by the FDA as a non-opioid analgesic peptide against long-term neuropathic pain in human, under the commercial name of Prialt [49]. ω-CTX solidified a role in pain management with the approval of ziconotide [50]. Ziconotide acts as a selective N-type voltage-gated Ca^{2+} channel blocker. This action inhibits the release of pro-nociceptive neurochemicals like glutamate, CGRP, and substance P in the brain and spinal cord, resulting in pain relief. With very similar structure to ω-CTX, RsXXIVA was isolated from the venom duct of Conus regularis and it showed inhibition on CaV2.2-mediated calcium currents in rat superior cervical ganglion (SCG) neurons, plus an analgesic effect on mice [49].

2.4 Marine neurotoxins interacting with other receptors

Among the CTX family some toxins bind to the receptors in nerves and muscles, with high affinity and highly specific features. Thus they can be used as useful tools for neuroscience. Such as α-CTX can acts on and blockades neuronal chondrocyte acetylcholine receptors (AchR) [51].

Domoic acid (DA) is produced by a type of algae called Pseudo-nitzschia, which flourished in massive blooms due to above average water temperatures and high levels of nutrient runoff [52]. DA from algae induced sea lions death and is found in various commonly consumed commercial fish species [53]. Exposure to DA damages the spatial memory of sea lions. It is also the principal cause of amnesic shellfish poisoning (ASP) in human. DA behaves similarly to the neurotransmitter glutamic acid, binding to and eventually killing receptors in the hippocampus and causing short- and long-term memory loss in mammals, including humans [54]. Thus fast and effective method was developed to detect

DA based upon microchip electrophoresis combined with laser-induced fluorescence detection [55]. It has been widely used as AMPA/kainate receptor agonist in neurotoxicity studies in learning and memory disease models [6, 56, 57]. Recent study indicate that DA induces long-term changes in α2-adrenoceptor binding in rat brain that may have relevance to the progression of an epilepsy phenotype [58].

The neurotoxin β-N-methylamino-L-alanine (BMAA) and its isomers 2,4-diaminobutyric acid (DAB) and N-2 (aminoethyl) glycine (AEG) are found in marine mollusks, probably produced by cyanobacteria [59]. BMAA has been hypothesized to trigger the pathogenesis of neurodegenerative diseases like Amyotrophic Lateral Sclerosis (ALS) and Alzheimer's disease (AD). Extensive in vitro experiments have demonstrated that the neurotoxicity of BMAA for neurons is a result of multiple mechanisms including action on glutamate receptors to induce oxidative stress in the neuron by depleting glutathione and generating a cytotoxic DNA damaging alkylating agent [60, 61]. Study with vervets showed that BMAA may trigger neurodegenerative disease such as Alzheimer's Disease as a result of gene/environment interaction, thus it could became a useful tool for studying of neurodegenerative disease [62, 63]. Because it is predicated that BMAA toxicity is transferrable from mother to infant, thus extra caution is in need within the areas where BMAA and its derivatives exist [64, 65]. Method to detect BMAA level will facilitate prevention of BMAA toxicity [66].

Nereistoxin (NTX) was originated from a marine annelid worm Lumbriconereis heteropoda. There have been reports about its neuronal toxicity in human and animal by blocking nicotinic acetylcholine receptor, and by reversibly inhibiting radio ligand binding to Torpedo nicotinic receptors [67, 68]. It causes significant neuromuscular toxicity, that may result in respiratory failure. There is report that in chick retinas NTX blockaded retinal responses to the nicotinic agonist dimethylphenylpiperazinium [69]. NTX inhibition characterized of being selective for nicotinic receptors, long lasting, and not reversible upon washing. NTX or its metabolite is suggested to be a potent antagonist as well as a selective reducing agent for nicotinic receptors in chick retina. Its analogue pesticides including cartap, bensultap, thiocyclam, and thiobensultap have been commonly used in agriculture, because of their low toxicity and high insecticidal activity [70].

Anabaseine is an alkaloid toxin produced by Nemertines. Due to its similar structure with nicotine, it has been shown to act as an agonist on most nicotinic acetylcholine receptors in the central nervous system and peripheral nervous system [71]. Binding of the receptors causes the depolarization of neurons and induces the release of both dopamine and norepinephrine. Compare to existing antipsychotic drugs, α7-Nicotinic acetylcholine receptors have became as a potential therapeutic target for the treatment of neurocognitive dysfunctions in schizophrenia [72]. However its derivatives, such as 3- (2,4 dimethoxy) - benzylidene。-anabaseine (DMXB-A, known as GTS-21), with cytoprotector properties and improved memory in experimental animal of cognitive and memory deficits diseases [73]. Substances of this series are developed as potential drugs for treating Alzheimer's disease.

3 CONCLUSION

We summarized the mechanism of most popular marine neurotoxins by far and updated their pharmacology characters and applications in research. Research in marine neurotoxins is very important for people's health. Based on the current information about marine toxins, a platform should be established to detect the neurotoxicity of marine active substrates. It is important to monitor the safety of marine products. Studies investigating applications of marine toxins in neurodegenerative diseases, the development of biosensors is also of great interest. Marine neurotoxins can be used as experimental models, potential therapeutics, or neurobiological tools. As a conclusion, due to the unique features of marine neurotoxins and strong biological activities, they can play an important role in the brain science research and great potential for drug development.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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