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CONOTOXINS- POTENTIAL MARINE SUBSTANCES: AN OVERVIEW

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Abstract: Cone snails are predatory marine animals that kill their prey with powerful venom. Conotoxins are a pharmacologically and chemically diverse group of toxins found in the venom. A number of species of cone snails, such as *Conus geographus*, are deadly to humans. Conotoxins affect numerous neurotransmitter receptors and ion channels in the body. Conotoxins produced by cone snail contain a tremendously diverse natural pharmacology. Conotoxins contains hundreds of different compounds, and its exact composition varies widely from one species of cone snail to another. Some cone snail venoms also contain a pain-reducing toxin, which the snail uses to pacify the victim before immobilising and then killing it.Concerns in the homeland security field exist that certain conotoxins could be weaponized and used an aerosol. Conotoxins at risk of terrorist use include α-conotoxins, κ-conotoxins and δ-conotoxins. Most conotoxins are not a bioterrorism threat.

Keywords: Conus, Conotoxin, Neurotoxin, Terrorism.

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INTRODUCTION

The cone snail is a marine predatory snail that uses powerful venom to kill its prey [1]. Cones are a type of sea snails that belong to Conus, which is a large genus of small to large, predatory sea snails and marine gastropod molluscs. Cone snails are mostly tropical in distribution. There are over 500 different species of cone snails. They are all venomous to

one degree or another. These unique marine organisms deliver their complex venom through a specialized radular tooth that serves as both a harpoon and disposable hypodermic needle. The venom is an extremely complex concoction of 20-200 components composed mostly of modified peptides (conopeptides) [2]. Cone snails belong to the phylum Mollusca, the class Gastropoda, the order Sorbeoconcha, and the family Conidae, and the genus *Conus* [3]. The shells of the cone snails are spiral and conic, hence their name. Cone snails are found in warm seas and oceans throughout the world but are mostly in the Indo-West Pacific region [4]. The siphon is the "nose" of the cone snail. The siphon is used for detecting prey and for respiration. The proboscis is the hunting tool used by the snail. The proboscis is a long tubular muscular elongation of the mouth. In the proboscis are harpoons containing the toxins [5]. Among the deadliest of all cone snails, Conus geographus has an unusual strategy for catching fish: it is believed to prey primarily on schools of small fish hiding in reef crevices at night. It approaches potential prey with its false mouth highly distended, which is used as a net. It is believed to engulf multiple fish, and once the fish are enclosed within the gargantuan false mouth, it harpoons each fish, simultaneously injecting venom. The paralyzed prey are predigested within the false mouth, with the scales and bones of the fish regurgitated after 1–2 hours; the pre-digested soft parts of the fish are then moved further into the gut for complete digestion and absorption [6]. Several peptides from Conus geographus venom have become widely used in neuroscience research [7]. A conotoxin is one of a group of neurotoxic peptides isolated from the venom of the marine cone snail, genus *Conus*. Conotoxins, which are peptides consisting of 10 to 30 amino acid residues, typically have one or more disulfide bonds. Conotoxins have a variety of mechanisms of actions, most of which have not been determined. However it appears that many of these peptides modulate the activity of ion channel [8]. The action of the conotoxins occurs by blockage of muscular and neural receptors. There are two different toxin effects in the venom. The first, the "lightning-strike" effect, causes immediate immobilization of the injected prey through peptides that inhibit voltage-gated sodium channel inactivation, as well as peptides that block potassium channels. Together, this combination results in a massive depolarization of any axons in the immediate vicinity of the

venom injection site, causing an effect similar to electrocuting the prey. The second effect is achieved more slowly and involves total inhibition of neuromuscular transmission through conopeptides, which act at sites remote from the venom injection site, such as neuromuscular junctions [9]. The toxins from the fish hunting cone snails are also more bioactive upon the human system than the mollusk hunting cone snails, with deaths having occurred. The synthesis of the conotoxins takes place in the epithelial cells of the venom duct and then secreted into the lumen of the venom duct. Attached to the venom duct is the venom bulb. The function of the venom bulb is to contract and push venom into the harpoon [3].

EXPOSURE OF CONE SNAILS

A sting by certain species of cone snails are poisonous to humans including *Conus geographus, Conus catus, Conus aulicus, Conus gloria-maris Conus omaria, Conus magus, Conus striatus, Conus tulipa,* and *Conus textile, Conus geographus* is the most lethal to humans [10]. Piscivores are more dangerous to humans than other cone snails [11,12]. Signs and symptoms of exposure include faintness, ptosis (drooping eyelids), poor coordination, absent gag reflex, areflexia, paresthesias (abnormal sensations such as burning or tingling), urinary retention, diplopia (double vision), blurred vision, speech difficulties, dysphagia (difficulty swallowing), weakness, nausea, generalized numbness, and respiratory arrest [10-14]. Autopsy findings may include blanching and swelling at the site of injection, petechial hemorrhages, cardiac dilation, and cerebral edema [13]. No specific antidotes are available.

CONOTOXINS

Laboratory studies found venom from *Conus geographus* to cause convulsions and respiratory suppression (without immediate concurrent cardiac arrest) in mice. In isolated muscles venom from *Conus geographus* produced muscle paralysis [15,16]. Conotoxins work on a variety of neurotransmitters in the body including glutamate, adrenergic, serotonin, and cholinergic and ion channels of sodium, potassium and calcium [17]. The chart below indicates the known neurotoxic peptides in the venom, and their actions. It is designed to be delivered directly into the cerebrospinal fluid by means of a small pump. The number of conotoxins whose activities have been determined so far is five, and they are called α (alpha)-, δ (delta)-, κ (kappa)-, μ (mu)-, and ω (omega) [18].

Table 1. Pharmacological Classes of conotoxins[18]

Family	Physiological Effects
Alpha (α)	Blocks nicotinic receptors. Produces muscle paralysis
delta (δ)	Inhibits the fast inactivation of voltage gated sodium channels.
epsilon (ε)	Affects presynaptic calcium channels needed for action potential activity.
iota (ι)	Agonist at sodium gated channels with no delayed inactivation.
kappa (κ)	Antagonist of potassium gated channels. Interferes with repolarization.
mu (μ)	Antagonist of sodium gated channels.
rho (ρ)	Impacts alpha-adrenal receptors affecting blood pressure and smooth muscle.
sigma (σ)	Affects serotonin activity. Impacts mood, appetite and stress control
chi (χ)	Affects neuronal adrenergic transporter.
omega (ω)	Works on voltage gated calcium channels.
Conantokins	Antagonize glutamate, the main excitatory neurotransmitter in the brain, at N-methyl-D-aspartate receptors.
Conopressins	Modulate vasopressin/oxytocin receptors. Increases blood pressure.

One of the key components to the venom of *Conus geographus* are the α-conotoxins [19]. The α-conotoxins are antagonists of nicotinic receptors. Nicotinic receptors serve a variety of functions in the body. Nicotinic receptors are needed for the

contraction of skeletal muscle. Acetylcholine is released by a motor neuron. The acetylcholine then attaches to the nicotinic receptors on the muscle. This starts a physiological cascade causing the muscle to contract. Physically blocking the nicotinic receptor with a drug or toxin would stop the contraction and cause paralysis. The diaphragm is a muscle located below the lungs and divides the abdomen from the chest cavity. The diaphragm is the primary muscle that causes the lungs to inflate and deflate. Paralysis of the diaphragm results in the cessation of breathing. The diplopia reported from human exposures probably results from paralysis of the extraocular muscles. Nicotinic receptors are the main receptors at ganglia synapses. Nicotinic receptors are also found in the brain. The first isolated α-conotoxins were GI, GIA, and GII and found in *Conus geographus* [19]. These α-conotoxins do not affect the central nervous system. Other alpha-conotoxins were isolated different species including *Conus magus, Conus striatus, Conus consors, Conus achatinus,* and *Conus spurious* [20]. A number of α-conotoxins were found to have activity on the nicotinic receptors in the brain. The first centrally acting α-conotoxin was α-conotoxin CTx IMI isolated from *Conus imperialis*, a worm-eater [20].

CONOPEPTIDES

Marine snails have the prettiest shells on their backs and the deadliest poison in their sting. The potent armamentarium of the *Conus* snails includes conotoxins, a fascinating series of peptides. These peptides, known as conopeptides, have been optimized through evolution to target specific ion channels and receptors with very high affinities and selectivities [21]. The peptides possess pharmacological properties that make them valuable tools for pain therapy and certain disorders of the central nervous system.

STRUCTURE OF CONOPEPTIDES

The peptides are merely 10–40 residues and therefore smaller than most known protein toxins. These linear peptides tend to be girded by several disulphide bonds making them structurally rigid. They also have a large number of post-translational modifications, some of which are unusual. This has given rise to about 50,000 sequences in the estimated 500 species [8]. This cocktail of peptides targets a diverse range of voltage-sensitive sodium, calcium, and potassium channels and *N*-methyl-d-aspartate, glutamate, vasopressin, serotonin, and acetylcholine receptors, which leads to an immediate and efficient immobilisation of the prey [22].

MEDICINAL APPLICATIONS OF CONOTOXINS

Conotoxins are used as tools of research including determining how specific receptors and ion channels work. Conotoxins have potential roles in the direct treatment of disease. The ω-

conotoxins are used in neuroscience research to study calcium channel subtypes [23]. A variety of conotoxins are used to understand specific sodium channels. A number of potential pharmaceuticals are being derived from conotoxins. Ziconitide is derived from *Conus magus* ω-conotoxin MVIIA. Centrally acting α-conotoxins in theory could be useful in treating Alzheimer's disease, nicotine addiction, and in pain management [20]. Prospective therapeutic or research uses of conantokins include pain, epilepsy, stroke, and Parkinson's disease. The chi family inhibits norepinephrine transport and thus is potential treatments for attention-deficit/hyperactivity disorder or depression [24].

CONOTOXINS AND TERRORISM

Conotoxins have potential as biological weapons [25,26]. The direct chemical synthesis would more likely be found in clandestine laboratory than the farming of cone snails.

Potential methods of using of conotoxins in terrorism include contamination of food sources or aerial dispersal in a concentrated population area. The most likely method of dispersal would be as an aerosol [26]. Information on the inhalation effects of conotoxins is not available in the public domain. The onset of effects from inhaling conotoxins would probably be much faster than from cone snail stings assuming adequate absorption of the toxin in the lungs. Conotoxins are not volatile and need to be aerosolized. One barrier is creating the conotoxins as an aerosol is the developing the optimal particle size of 1 to 3 μm [27]. The mu family, the omega family, and NMDA antagonists are low risk for a bioterrorism incident [28]. Serotonin acting conotoxins are poor candidates for weaponization because obtaining lethal toxicity with serotonergic agents is difficult. The main predicted effect of adrenergic acting conotoxins based on the receptor activity would be a rapid increase in blood pressure. In theory, terrorists could also use certain conotoxins to disrupt agriculture by poisoning farm animals [29].

RISK FACTORS

The δ-conotoxins are also high risk because of the excitotoxicity and prolonged muscle contractions. κ-conotoxin PVIIA could cause cardiac toxicity by blocking the potassium channels in the heart [30].

CONCLUSION

Conotoxins play an important role in medical field. conotoxins is one of the attributes that make them diagnostic tools in the characterization of neural pathway, as therapeutic agents in medicine, and potentially as biodegradable toxic agents in agroveterinary applications. Conotoxin is widely used in the pain relief since cancer is a multi-factorial condition, treatment has to be go beyond merely removing the tumor. Most conotoxins are not a bioterrorism risk. The α-conotoxins, κ-conotoxins and δ-conotoxins pose the greatest risk as

terrorist threat. Potential effects include muscle paralysis, muscle contractions, or other effects from altering ion channels in cardiac, nerve, or muscle cells. Numerous technical hurdles need to be overcome to weaponize the conotoxins.

REFERENCES

1. Wilkins WK Facts about cone shells. Helium.

2. Newcomb R. and Miljanich G: Neurotoxins of Cone Snail Venoms Handbook of Neurotoxicology. 2002; 617-651.

3. http://www.theconesnail.com/meet-the-snails/taxonomy

4. http://www.theconesnail.com/explore-cone-snails

5. http://www.theconesnail.com/explore-cone-snails/prey/piscivores

6. Johnson CR and Stablum W: Observations on the Feeding Behavior of Conus geographus (Gastropoda: Toxoglossa). Pac Sci 1971; 25:109–111.

7. Olivera BM, Miljanich GP, Ramachandran J and Adams ME: Calcium channel diversity and neurotransmitter release: the omega-conotoxins and omega-agatoxins. Annu Rev Biochem 1994; 63:823–867.

8. Terlau H and Olivera BM: Conus venoms: A rich source of ion channel-targeted peptides. 2004; Physiol. Rev 84:41–68.

9. Cruz LJ, White J. Handbook of Clinical Toxicology of Animal Venoms and Poisons. 1995; 117–127.

10. http://emedicine.medscape.com/article/769638-overview#a0199

11. Haddad V, Paula Neto JB and Cobo VJ: Venomous mollusks: the risks of human accidents by conus snails (gastropoda: conidae) in Brazil. Rev Soc Bras Med Trop 2006; 39: 498-500.

12. Fegan D and Andresen D: Conus geographus envenomation. Lancet 1997; 349: 1672.

13. Rice RD and Halstead BW: Report of fatal cone shell sting by Conus geographus Linnaeus. Toxicon 1968; 5: 223-224.

14. Fernandez I, Valladolid G, Varon J and Sternbach G: Encounters with venomous sea-life. J Emerg Med 2011; 40: 103-112.

15. Whyte JM and Endean R: Pharmacological Investigation of the Venoms of Marine Snails Conus Textile and Conus Geographus. Toxicon 1962; 1: 25-31.

16. Endean R, Parish G and Gyr P: Pharmacology of the venom of Conus geographus. Toxicon 1974; 12: 131-138.

17. Olivera BM, Rivier J, Scott JK, Hillyard DR and Cruz LJ: Contoxins. J Biol Chem 1991; 266: 22067-22070.

18. Classification Schemes Used in Conoserver. Conoserver.

19. Gray WR, Luque A, Olivera BM, Barrett J and Cruz LJ: Peptide toxins from Conus geographus venom. J Biol Chem 1981; 256: 4734-4740.

20. Azam L and McIntosh JM: Alpha-conotoxins as pharmacological probes of nicotinic acetylcholine receptors. Acta Pharmacol Sin 2009; 30: 771-783.

21. Shen GS, Layer RT and McCabe RT: Conopeptides: From deadly venoms to novel therapeutics., Drug Discov Today 2000; 5:98-106.

22. Olivera BM, Rivier J, Clark C, Ramilo C, Corpuz GP, Abogadie FC, Mena EE, Woodward SR, Hillyard DR and Cruz LJ: Diversity of Conus neuropeptides. Science 19990; 249: 257–263.

23. Becker S and Terlau H: Toxins from cone snails: properties, applications and biotechnological production. Appl Microbiol Biotechnol 2008; 79: 1-9.

24. Essack M, Bajic VB and Archer JA: Conotoxins that confer therapeutic possibilities. Mar Drugs 2012; 10: 1244-1265.

25. Anderson PD: Bioterrorism: toxins as weapons. J Pharm Pract 2012; 25: 121- 129.

26. http://www.cbwinfo.com/Biological/Toxins/Conotox.html

27. Roy CJ, Reed DS and Hutt JA: Aerobiology and inhalation exposure to biological select agents and toxins. Vet Pathol 2012; 47: 779-789.

28. http://www.selectagents.gov/Select%20Agents%20and%20Toxins%20Exclusions.html

29. http://www.selectagents.gov/Select%20Agents%20and%20Toxins%20List. Html

30. International Cyanide Management Code for the Gold Mining Industry. Environmental and Health Effects of Cyanide.

31. Centers for Disease Control and Prevention. Botulism: Background Information for Clinicians. Emergency Preparedness and Response.

32. Zhang JC, Sun L and Nie QH: Botulism, where are we now Clin Toxicol (Phila) 2010; 48: 867-879.

33. Peter D. Anderson and Gyula Bokor: Conotoxins: Potential weapons from sea J Bioterr Biodef 2012, 3: 1-4.

34. Hao Hu, Pradip K and Mark Yandell: Elucidation of the molecular envenomation strategy of the cone snail Conus geographus through transcriptome sequencing of its venom duct BMC Genomics 2012; 284: 1-23.