

# NEUROTOXIPEDIA

## An overview of pre- and postsynaptic neurotoxins



Flickr © All rights reserved, kindly provided by Bastian Kranz-Rudolph

### VENOMOUS AIN'T ALWAYS VENOMOUS

Snake venoms can be high potent in order to fight predators or competitors and seize prey. That's because venoms are highly complex and contain a mixture of diverse toxins, enzymes, polypeptides, nucleotides and

other substances [1, 3]. Imagine a venom is like a fruit salad, that consists of different types of fruits, which vary in size and form. Some highly potent components are called neurotoxins, which affect the nervous system. Elapids are high potent neurotoxic snakes, their venom consist of a full range of highly effective neurotoxins [4]. The neurotoxicity of a snake bite is often life-threatening and therefore it is important to understand the mechanisms of snake venoms [3].

Neurotoxins affect the neuromuscular junction (NMJ), the place where the nerve cells and muscle cells are "communicating". This leads to a defective communication between nerve cell terminus and muscle cells [1].

Hey Taipi!  
What is Neurotoxicity?

It'ssss the capacity of my venom  
to cause adverse effects on your  
nervous system!



### HOW DO NERVE CELLS AND MUSCLE CELLS COMMUNICATE?

In order to understand the neurotoxic effects of the snake venom, it is important to understand what's happening on the NMJ. An electronic impulse on the presynaptic terminus leads to the release of the neurotransmitter Acetylcholine (ACh, a chemical "communication messenger") into the synaptic cleft. The following binding of ACh to the postsynaptic muscle ACh-Receptors leads to signal transmission and muscle contraction (Fig. 1).

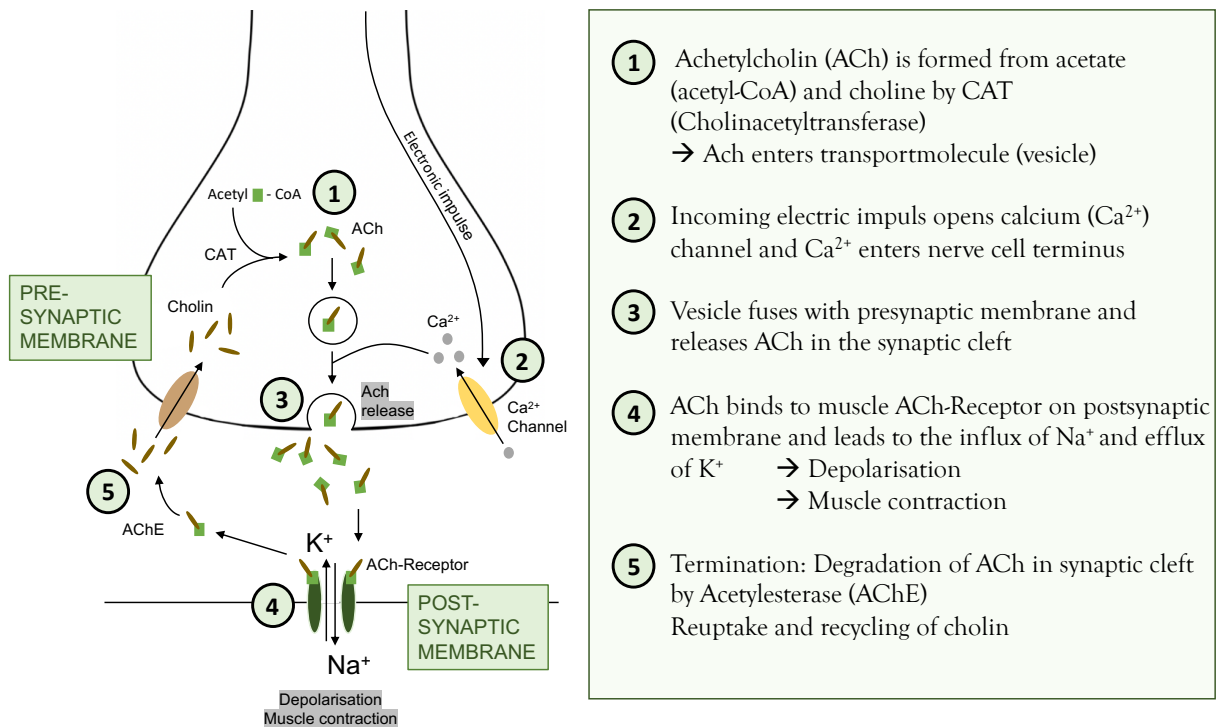


Figure 1: Events on the neuromuscular junction. Adopted from [1, 2].

## PRE- AND POSTSYNAPTIC NEUROTOXINS

The neurotoxins in elapids can be divided into two main groups, the presynaptic neurotoxins ( $\beta$ -neurotoxins) and the postsynaptic neurotoxins ( $\alpha$ -neurotoxins). Presynaptic neurotoxins affect the presynaptic nerve terminal, which is responsible for the production, package, transport and release of ACh. Postsynaptic neurotoxins bind on the postsynaptic ACh-Receptor and therefore block the binding of ACh. Both neurotoxin groups cause a dysfunction of the NMJ including paralysis, the loss of muscle function and respiratory failure, among other things [1].

### Mode of action of pre- and postsynaptic neurotoxins

<p><b>3 Presynaptic neurotoxins [1,5]</b></p> <p><b><math>\beta</math>-bungarotoxin (krait)</b> <b>taipoxin (taipan)</b> <b>notoxin (Australian tiger snake)</b></p> <ul style="list-style-type: none"> <li>❖ Toxin can enter ACh vesicle during ACh release</li> <li>❖ Phospholipase <math>\text{A}_2</math> activity</li> <li>❖ Depletion of vesicle phospholipids               <ul style="list-style-type: none"> <li>→ Depletion of synaptic ACh vesicles</li> <li>→ Inhibition of NMJ transmission</li> <li>→ Degeneration of NMJ</li> </ul> </li> </ul>	<p><b>4 Postsynaptic neurotoxins [1]</b></p> <p><b><math>\alpha</math>-bungarotoxin (krait)</b> <b><math>\alpha</math>-cobratoxin (cobra)</b> <b>candoxin (krait)</b></p> <ul style="list-style-type: none"> <li>❖ Non-depolarising block of postsynaptic ACh-Receptor (<u>irreversible</u> or competitive)               <ul style="list-style-type: none"> <li>→ No Depolarisation of the muscle cells</li> <li>→ Inhibition of the muscle contraction</li> </ul> </li> </ul>
--	---

In addition, some snake venom neurotoxins alter the NMJ transmission through different mechanisms e.g. through the block of Acetylcholinesterase (synaptic cleft) or the postsynaptic depolarizing block of ACh-Rezeptor.

- However, snake venoms do not only contain a single neurotoxin. Most venoms are composed of many different pre- and postsynaptic neurotoxins, which explain the complexity of their multiple actions.

**As an example**, the venom of the **krait (Bungarus spp.)** contains  $\alpha$ -,  $\beta$ - and  $\kappa$ -bungarotoxin, as well as candoxin. As a mixture they block presynaptic through the depletion of ACh vesicle ( $\alpha$ -bungarotoxin), as well as post-synaptic through an irreversible ( $\beta$ -bungarotoxin) and reversible (candoxin), non-depolarising block of the muscle ACh-receptor.  $\kappa$ -bungarotoxin blocks neuronal ACh-receptors in autonomic ganglia.

## REFERENCES

1. Ranawaka, U.K., D.G. Lalloo, and H.J. de Silva, *Neurotoxicity in snakebite—the limits of our knowledge*. PLoS neglected tropical diseases, 2013. 7(10): p. e2302.
2. Rang, H.P., et al., *Rang & Dale's Pharmacology*. Vol. 6. 2007: Elsevier Health Sciences: p. 244-250.
3. Kuruppu, S., et al., *Neurotoxins from Australo-Papuan elapids: a biochemical and pharmacological perspective*. Critical reviews in toxicology, 2008. 38(1): p. 73-86.
4. Hodgson, W.C. and J.C. Wickramaratna, *Snake venoms and their toxins: an Australian perspective*. Toxicon, 2006. 48(7): p. 931-940.
5. Montecucco, C. and O. Rossetto, *How do presynaptic PLA2 neurotoxins block nerve terminals?* Trends in biochemical sciences, 2000. 25(6): p. 266-270.