

## the poison in pain

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Pain is a persuasive way of keeping the enemy at bay. Hosts of living beings make use of it, both in the animal and the plant world. Many of us have experienced the sting of a nettle, or indeed a wasp, a cat's scratch and perhaps even the nip of a spider. And who hasn't used the end of their foot to assign a kick or two, right where it hurts? Besides spitting out a few venomous words... Not many of us, however, have actually come across a snake and the twang of its venom. As we all know – or have been told – a snake's bite can vary from being a little uncomfortable to excruciatingly painful and even harmful, not to mention fatal. Over the millennia, a snake's venom has been perfected and become a highly specialised cocktail of hundreds, even thousands, of molecules – most of which are proteins. Recently, scientists discovered a neurotoxin – dubbed MitTx – that causes pain via acid-sensing ion channels which run along the membranes of neurons. A novelty in the world of nociception.



Son Snake, by Amelia Hirschauer  
(Australia)

Courtesy of the artist

A snake's venom is saliva that has become specialised in being nasty to anyone or anything that has the misfortune of being injected with it. It is synthesized in venom glands and then inoculated into the snake's victims through its fangs, which have been designed so as to sink with ease into the flesh of a predator or prey. Snake venom is a potion with many powers – it can make blood coagulate, damage veins, interfere with a heartbeat, modify membrane permeability,

cause numbness, paralysis, and even death. And these many powers are the fruit of as many different chemical entities, most of which are proteins.

Charles Lucien Bonaparte (1803-1857) – one of Napoleon Bonaparte's many nephews and a biologist in his time – was the first to observe that venom was mainly proteinaceous in nature. Since then, many toxins – of all sorts – have been characterised. Amongst which the neurotoxins, i.e. toxins which have an effect on neurons and are able to cause insults such as mental retardation, memory impairment, epilepsy, paralysis or dementia to name a few.

This said, though neurotoxins can be very detrimental to those who receive them, they are a precious source for researchers who seek to understand how the central and the peripheral nervous systems work. And, when you get an understanding of how part of such complex networks behave, you can then attempt to design drugs which can counter instances such as memory loss, limb paralysis ...and pain.

Indeed, pain is what the neurotoxin MitTx has to offer. This particular neurotoxin is part of the Texas coral snake's venom (*Micrurus tener tener*) whose fangs offer intense and continuous pain by injecting poison which is able to excite a group of sensory neurons. MitTx is a heteromeric complex of two subunits: Neurotoxin MitTx-alpha and Phospholipase A2 homolog Tx-beta. And though the alpha subunit carries the neurotoxin qualifier, it is unable to carry out its neurotoxin function without its fellow beta subunit – and vice versa.

Though very little is known about MitTx and how exactly it affects sensory neurons, it has offered scientists new insights into the sensation of pain and the, as yet, unknown role of acid-sensing ion channels (ASICs) in being part of it. Indeed, MitTx seems to bind to the extracellular part of ASICs, thus causing an immediate boost in cellular calcium. How this neuronal depolarization occurs remains a mystery but it may have something to do with the lipid-binding trait of the beta subunit. What is more, depolarization is not only potent but also very long – which

echoes the potency and prolongation of the sensation of pain.

It is thought that the strength of the pain may have something to do with the affinity of the alpha/beta complex, and not with the actual bonding of the neurotoxin to the channel. Much remains to be understood though. ASICs are not unknown to the effects of toxin – tarantulas, for instance, produce toxins that target ASICs. However, these toxins lock the channels in a desensitised state: which is exactly the opposite of what MitTx does!

Whatever the mechanism, MitTx and ASICs provide novel insights into the world of nociception. Toxins will always be a mine of information for understanding the ins and outs of pain since Nature will always aim for the centres that produce it. And the bigger the pain, the greater the response. Conversely, scientists will be able to refine their research and design drugs that are more and more subtle for alleviating all sorts of pain, caused by all sorts of ailments. Save perhaps the pain inflicted by words.

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**N.B.** Read also Protein Spotlight issue 82, “The power behind pain” and Protein Spotlight issue 102, “Silent pain”

### Cross-references to UniProt

Phospholipase A2 homolog Tx-beta, *Micrurus tener tener* (Texas coral snake): G9I930  
Neurotoxin MitTx-alpha, *Micrurus tener tener* (Texas coral snake): G9I929

### References

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