

Coral snake venom reveals a unique route to lethality

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Rare coral snake *Micrurus mipartitus*. Credit: Alejandro Solórzano

For more than a decade, a vial of rare snake venom refused to give up its secret formula for lethality; its toxins had no effect on the proteins that

most venoms target. Finally, an international team of researchers figured out its recipe: a toxin that permanently activates a crucial type of nerve cell protein, preventing the cells from resetting and causing deadly seizures in prey. The details will be published online in the *Proceedings of the National Academy of Sciences* the week of Feb. 9.

"What we found are the first known animal toxins, and by far the most potent compounds, to target GABA(A) receptors," says Frank Bosmans, Ph.D., assistant professor of physiology and neuroscience at the Johns Hopkins University School of Medicine. "Once they bind to the receptors, they don't let go."

Biochemical studies revealed the identity of the venom's active ingredient: it's actually twin proteins, dubbed micrurotoxins (MmTX) after their serpentine source, the reclusive coral snake *Micrurus mipartitus*. Most toxins in snake venoms target specialized [nicotinic acetylcholine receptors](#) on the surface of [nerve cells](#) that make muscles contract, paralyzing the snakes' victims. But when the researchers tested MmTX on lab-grown cells saturated with nicotinic acetylcholine receptors, nothing happened. This was puzzling because, in mice, MmTX was known to cause a repeating pattern of relaxation and seizures, similar to what's seen in epilepsy.

By tagging the protein with a radioactive label, the team at Aix Marseille University was able to find out what protein it acted on. To the team's surprise, MmTX binds to GABA(A) receptors—pores on nerve cells in the brain and spinal cord. GABA(A) receptors' job is to respond to the molecule GABA by opening to let negatively charged chloride ions flow into a nerve cell that has just fired. Doing so resets the cell's equilibrium so that it can fire another signal when needed.

Further testing showed that MmTX binds to GABA(A) receptors more tightly than any other compound known—100 times tighter than the

plant-derived compound PTX, for example. MmTX also binds to a unique site on the GABA(A) receptor protein. Binding at that site changes the receptor's shape, making it far too sensitive to GABA molecules. When GABA binds, the receptor's pore opens permanently and the nerve cell is never able to reset, causing it to misfire, convulsing the animal and potentially causing death.

"Anti-anxiety medications like diazepam and alprazolam bind to GABA(A) receptors too, but they cause relaxation instead of seizures because they bind much more loosely," says Bosmans. His team plans to use MmTX as a tool for learning more about how GABA(A) receptors work. Since errors in the [receptors](#) can cause epilepsy, schizophrenia and chronic pain, the team hopes that their future work will be able to shed light on these and other disorders.

More information: MmTX1 and MmTX2 from coral snake venom potently modulate GABAA receptor activity, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1415488112

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