

Snakes in evolutionary arms race with poisonous newt

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Smooth newts (*Lissotriton vulgaris*). Credit: Museum Victoria

The rough-skinned newt is easily one of the most toxic animals on the planet, yet the common garter snake routinely eats it. How does a newt which produces enough toxin to kill several grown humans almost immediately manage to become prey in the food chain?

The answer comes in the form of an evolutionary arms race that pits the toxin of the newt, tetrodotoxin or TTX, against the voltage-gated [sodium channels](#) of the snake. The newt's toxin typically blocks sodium channels, which are found in excitable tissue including muscles, nerves, brain, and heart, but garter snakes seem immune to its effects.

Joel McGlothlin, assistant professor of biological sciences in the College of Science at Virginia Tech with a team of scientists that included his former postdoctoral advisor Edmund Brodie III of the University of Virginia, looked for clues to the evolution of TTX resistance in the DNA sequences of garter snake sodium channels.

"There are nine different sodium channels in reptiles, found in different tissues of the body," McGlothlin said. "We knew when we started that muscle channels had evolved resistance to TTX in garter snakes, and we predicted that many of the others should have too. If you're going to eat poison, you not only need to have muscles that work, the nerves that control them have to work too."

McGlothlin sequenced the DNA of five previously undescribed garter snake sodium channels and examined them for signatures of TTX resistance. Of these, three are found primarily in the brain and two are found in motor and sensory nerves outside the brain. The brain channels had not evolved resistance to TTX at all.

"The brain is protected by the blood-brain barrier, so it makes sense that these channels wouldn't have evolved resistance" he said. Many chemicals can't cross this barrier, which separates the fluid around the brain and spinal column from the rest of the body. TTX is one of the things that can't cross.

"The two nerve channels outside the brain, however," McGlothlin said, "have both evolved resistance to the toxin, and they've done so independently. When we compared the DNA sequences to a closely related lizard, there were changes unique to the snakes that should provide resistance to the toxin."

The paper, published in the journal *Molecular Biology and Evolution*, shows that at least three sodium channels contribute to resistance to

TTX: NaV1.4 in muscle, NaV1.6 in rapid-firing neurons, and NaV1.7 in sensory neurons involved with smell and pain sensation.

Only garter snakes on the west coast have resistant muscle channels, where they live in proximity to the toxic rough-skinned newts. However, the team showed that resistant nerve channels are found in all garter snakes, even in areas without highly toxic prey.

"Garter snakes here in Virginia have the same resistant channels in their nerves, even though there are no rough-skinned newts around," McGlothlin said.

Virginia's red-spotted newts have much less TTX than their western cousins, and resistant nerves might be enough to protect garter snakes that eat them.

"The fact that all garter snake have resistant nerve channels suggests resistant nerves evolved earlier than resistant muscle," he said, "which might have allowed garter snakes to start eating really poisonous newts in the first place."

McGlothlin says the work shows that the molecular basis of adaptation is somewhat predictable.

"The evolution of toxin resistance was predictable based on the biology of the snake—only the channels that are vulnerable to the toxin evolved resistance. Also, we see changes in the similar regions of these three genes, which suggests they're evolving in similar ways in response to the same selection pressure."

The work has prompted McGlothlin to take a deeper look into evolutionary history as he suspects some of these sodium channels evolved resistance to TTX in the ancestors of [garter snakes](#) – perhaps as

long as 100 million years ago.

McGlothlin is currently examining the DNA sequences of the Nav gene family across snakes, lizards, and birds – some of which also count newts as a food source. "If we look at this gene family across all of these groups, we should be able to determine whether evolving resistant sodium channels is a general response to eating toxic prey or whether it is unique to snakes," he said.

Provided by Virginia Tech

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