Toxin sponges may protect poisonous frogs and birds from their own poisons, study suggests

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Phyllobates terribilis. Credit: Wilfried Berns Tierdoku.com / Wikimedia / CC BY-SA 2.0 de

A team of researchers from the University of California, San Francisco (UCSF), Stanford University, and the California Academy of Sciences (CAS) has uncovered new clues as to how poisonous frogs and birds avoid intoxicating themselves. Their study, which will be published August 5 in the *Journal of General Physiology* (*JGP*), suggests that, rather than evolving resistant versions of the toxin's target protein, the animals produce "toxin sponges" that can mop up the poison and prevent it from exerting its deadly effects.

Many poisonous animals protect themselves from predators with toxins that cause paralysis and cardiac arrest by binding to voltage-gated sodium channels, crucial proteins that mediate electrical impulses in neurons, muscle, and the heart. Batrachotoxin, for example, is an extremely potent sodium channel toxin found in poisonous *Pitohui* birds in New Guinea as well as several poison frog species in Colombia. The golden poison frog *Phyllobates terribilis* is estimated to carry 1 milligram of batrachotoxin in its skin glands, enough to kill between 10 and 20 humans.

But despite their having voltage-gated sodium channels of their own, *Pitohui* birds and poison frogs obtain batrachotoxin from the insects they eat and store the poison for long periods. How, then, do these animals avoid poisoning themselves?

One possibility is that the animals have evolved batrachotoxin-resistant sodium channels. "However, there haven't been any functional studies of poison frog or *Pitohui* sodium channels, so whether batrachotoxin-bearing animals rely on changes within their sodium channels or alternative resistance mechanisms remains unclear," says UCSF Professor Daniel L. Minor, Jr.

In the new study, Minor, postdoctoral fellow Fayal Abderemane-Ali, Justin Du Bois (Stanford University), Lauren O'Connell (Stanford

University), Jack Dumbacher (CAS), and colleagues demonstrate that *Pitohui* birds and *P. terribilis* frogs do not have batrachotoxin-resistant sodium channels. By comparing the effects of batrachotoxin with saxitoxin, a well-known paralytic shellfish toxin, Minor and colleagues suggest that these poisonous bird and frog species may instead rely on "sponge" proteins that mop up toxins and prevent their binding to sodium channels.

For the study, the team isolated sodium channels from both *Pitohui* birds and *P. terribilis*. They determined that they were highly sensitive to batrachotoxin. Frog sodium channels were, for example, sensitive to batrachotoxin levels more than 10 times below those found in *P. terribilis* in the wild.

A previous study reported that a mutation found in some poison frogs near the batrachotoxin-binding site can make rat sodium channels resistant to the toxin. Minor and colleagues introduced this mutation into the *Pitohui* and *P. terribilis* sodium channels and found that it failed to make the channels resistant to batrachotoxin. In fact, the mutation impaired the channels' function even in the absence of batrachotoxin. "Taken together, our observations challenge the idea that sodium channel mutation is the batrachotoxin autoresistance strategy for poisonous birds and poison frogs such as *P. terribilis*," Minor says.

Abderemane-Ali et al. propose that an alternative autoresistance mechanism is at play: the animals produce sponge proteins that mop up toxins and stop them from binding to sodium channels. Indeed, they found that, although batrachotoxin binds to isolated frog sodium channels, it doesn't seem to engage the channels when injected into living poison frogs.

Researchers have yet to identify any proteins capable of mopping up batrachotoxin. However, bullfrogs produce a protein called saxiphilin

that can tightly bind to the related poison saxitoxin. Minor and colleagues found that sodium channels isolated from *P. terribilis* are highly sensitive to saxitoxin, but this is reversed in the presence of saxiphilin.

"This demonstrates that high-affinity toxin-sponge proteins are able to prevent the actions of small molecule toxins that target sodium channels and lends support to the idea that toxin sequestration mechanisms may act to protect poisonous animals from autointoxication," Abderemane-Ali says.

Minor adds, "These sequestration strategies might not only offer a general means of toxin protection, but could also act in pathways involved in safely transporting and concentrating toxins in key defensive organs such as the skin. Understanding these pathways may lead to the discovery of antidotes against various toxic agents."

More information: Fayal Abderemane-Ali et al, Evidence that toxin resistance in poison birds and frogs is not rooted in sodium channel mutations and may rely on "toxin sponge" proteins, rupress.org/jgp/article-lookup … 0.1085/jgp.202112872

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