# Scorpion venom yields clues for developing better pharmaceuticals

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The molecular structures depicted above illustrate chemical changes that can turn a toxin in scorpion venom into a potentially beneficial compound. Credit: UC Davis School of Veterinary Medicine

Normally, people consider scorpions to be dangerous because of their venomous sting, but an international group of researchers recently discovered that a particular family of toxins, the calcins, found in some venom, might also have a unique beneficial function.

The breakthrough, announced this week in the journal *Proceedings of the*

*National Academy of Sciences*, explains what happens when a toxin produced by *Scorpio maurus*—a scorpion species found in North Africa and the Middle East—permeates the cell membrane. They also report why the toxin loses its potency once inside cells and may actually become healthful.

"This is the first time a toxin has been shown to chemically reprogram once inside a cell, becoming something that may be beneficial," said Isaac Pessah, a professor of molecular biosciences at the UC Davis School of Veterinary Medicine. "Being able to understand how this family of toxins lose their toxicity and become pharmacologically beneficial by changing activity towards the calcium channel target inside the cell is what's novel and may have translational significance."

## Calcium is key to cellular activity

The controlled release of calcium is a key step in many cellular processes.

"In any cell you can think of, calcium plays a role in shaping responses, activating or inhibiting enzymes, changing the shape of the cell or triggering cell division," Pessah said.

Calcium also is a key signal in both fertilization and programmed cell death. And, altered calcium regulation is a common step in many animal and human diseases. Pharmaceuticals that regulate cellular calcium homeostasis range from drugs for suppressing the immune system in organ transplant patients, to treatments for high blood pressure and heart disease.

## Investigating a paradox

Several years ago, Pessah began working with researchers from the Institute for Neurosciences in Grenoble France and the Pasteur Institute in Tunisia to isolate a specific toxin peptide called maurocalcin, which targets a calcium channel called the ryanodine receptor inside the cell. Maurocalcin is quite unusual in that it readily permeates into cells, while most other peptide toxins target more accessible receptors on the cell's surface.

"We therefore thought maurocalcin should be very toxic, since we previously showed that very low concentrations can completely stabilize an open (toxic) state of the ryanodine receptor and thereby upset a cell's calcium balance," Pessah said.

Maurocalcin, however, was seemingly benign once inside cells. Intrigued, the researchers set out to find the reason for this paradox. They discovered that once inside the cell, maurocalcin was modified by an enzymatic reaction called phosphorylation, a common cellular "switch" that normally turns reactions inside cells on or off by adding a phosphate group to a precise position on proteins.

## Potential toxin reprogrammed

This is the first example of a scorpion peptide being subjected to such modification once inside a mammalian cell. Phosphorylation of maurocalcin was found to completely reprogram its activity from that of a potential toxin to a potentially useful pharmacological tool.

"This is the real twist of nature," Pessah said. "The toxic peptide is not supposed to get inside cells, but it does, and then is phosphorylated, which not only neutralizes its toxicity but also reprograms its activity to be beneficial."

The research team further tested the plausibility and molecular details

responsible for pharmacological reprogramming by synthesizing artificial "phosphomimics," and studying their three-dimensional structures and how they modified ryanodine receptor channels.

Identifying the best synthetic substitutes for maurocalcin could pave the way for a novel strategy to control ryanodine receptor channels that leak calcium. Leaky ryanodine receptor channels are known to contribute to a number of human and animal diseases of genetic and/or environmental origins.

**More information:** Michel Ronjat et al. In cellulo phosphorylation induces pharmacological reprogramming of maurocalcin, a cell-penetrating venom peptide, *Proceedings of the National Academy of Sciences* (2016). DOI: 10.1073/pnas.1517342113

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