Tarantula toxins offer key insights into neuroscience of pain

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A Heteroscodra maculata, a West African tarantula.

When your dentist injects lidocaine into your gums, the drug blocks the pain of the oncoming drill, but it also blocks all other sensation – leaving your mouth feeling numb and swollen. What if there were a drug that could specifically block pain, but leave the rest of your sensations alone? In order to do this, you would need to find a way to control the cohort of nerve fibers that transmit the specific type of pain you would like to block.

A research team led by UC San Francisco scientists has discovered

molecules that may help researchers do just that: two toxins isolated from the venom of Heteroscodra maculata, a West African tarantula the size of your hand (commonly referred to as the "ornamental baboon" or "Togo starburst" tarantula). This spider's massive fangs deliver a poison that causes excruciating pain in part by triggering a specific kind of sodium channel within A-delta nerve fibers, according to the new research.

The study was led by researchers in the lab of David Julius, PhD, Chair of the Department of Physiology at UCSF, and was published June 6, 2016 in the journal *Nature*.

The researchers are excited about this finding for two equally important reasons: for opening a new chapter in our understanding of pain, and because the new toxins can now be used as a highly selective tool for manipulating this type of sodium channel, which also has been implicated in neurological disorders unrelated to pain, from epilepsy to autism to Alzheimer's disease.

"It's a good problem to have," said Jeremiah Osteen, PhD, the postdoctoral fellow in Julius's group who led the research team. "We didn't know which of the two findings we should be more excited about."

Julius's lab – which is renowned for the discovery and characterization of the so-called "wasabi receptor" – has recently been working to identify new pain pathways by screening more than a hundred different venoms from poisonous spiders, scorpions, and centipedes—sourced from the collection of co-author Glenn F. King, PhD, of the University of Queensland in Australia—all of which have evolved chemical defenses that target the biology of animals' pain nerves.

"There are dozens to hundreds of different active peptides in each

animal's venom," Julius said. "The deeper you look the more toxins there seem to be."

The Togo starburst tarantula's venom struck them as being particularly interesting because it appeared to activate a particular type of sodium channel within sensory nerves that was not a part of known pain pathways.

To identify which of the dozens of chemicals that made up the tarantula's venom were specifically targeting these channels, the researchers separated the venom and applied the components one-by-one to rodent sensory neurons in a lab dish. They found two peptide molecules that specifically and powerfully activated these sensory nerves , and experiments with lab-synthesized versions of the same molecules confirmed that these chemicals could activate pain-sensing neurons on their own.

Experiments with an array of different drugs that block candidate receptor molecules demonstrated that the two toxins specifically bind to and demonstrated that this particular receptor is indeed found on A-delta nerves in mice.

The accepted notion is that A-delta fibers may convey the sharp, immediate shock of a burn or a cut, ahead of the burning throb conveyed by slower C fibers. The newly discovered tarantula peptides allowed the researchers to isolate A-delta fibers in mice, and show that they also appear to play a role in touch hypersensitivity – when normally innocuous light touch causes discomfort – a type of pain common to diseases like shingles and many chronic pain syndromes.

Nine subtly different voltage-sensitive sodium channels

Additional experiments also implicated heightened touch sensitivity of Nav1.1-expressing nerves in a mouse model of irritable bowel syndrome, suggesting these nerves, and this channel, may play a role in the chronic discomfort such patients experience.

The pharmacological aspect of the research is also exciting for researchers because the nine subtly different voltage-sensitive sodium channels that are critical for nervous system function are extremely hard to manipulate individually. Researchers have been on a decades-long quest to find selective drugs for each subtype, so identifying two in one spider is a valuable find.

"These channels are incredibly hard to identify drugs for because the different subtypes are closely related, making it difficult to identify drugs or other agents that act on one subtype and not another," Julius said. "These toxins provide unique tools to start understanding exactly what this particular subtype, Nav1.1, does in terms of pain sensation."

The Nav1.1 subtype in particular has been implicated in the development of diseases including epilepsy, autism, and Alzheimer's disease, and the researchers hope that in addition to helping scientists understand the biology of pain, the new discovery will lead to the development of new drugs to target these diseases.

"These spiders had millions of years of evolution to come up with these potent and specific toxins," Osteen said. "They're tools one might be hard pressed to design as well in the lab."

More information: Jeremiah D. Osteen et al, Selective spider toxins reveal a role for the Nav1.1 channel in mechanical pain, *Nature* (2016). DOI: 10.1038/nature17976