Cone snail venom controls pain

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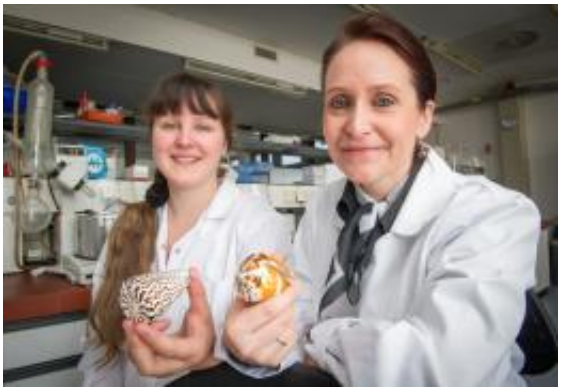

Foto: Volker Lannert/Uni Bonn

Components of the venom from marine cone snails can block the transmission of signals between nerve cells in minute quantities. This makes them potentially suitable for use as a novel analgesic. Researchers from the universities of Bonn and Jena, the Technical University of Darmstadt and the Leibniz Institute for Age Research in Jena have now identified the structure and action of various forms of mu-PIIIA conotoxin. They presented their results in the journal *Angewandte Chemie.*

Hidden in the mud, the cone snail *Conus purpurascens* lies in wait for its victims. It attracts its prey, fish, with its proboscis, which can move like a worm, protruding from the mud. Once a fish approaches out of curiosity, the snail will rapidly shoot a harpoon at it, which consists of an evolutionarily modified tooth. The paralyzed victim then becomes an

easy meal. It takes the venomous cone snail about two weeks to digest a fish. During this time, its venomous harpoon is also replaced.

Prof. Dr. Diana Imhof from the Pharmaceutical Institute of the University of Bonn, who is the project's PI, explained, "We are interested in the cone snail's neurotoxins, called conotoxins." They can be effective in minute quantities, interrupt the transmission of signals in nerve paths in a highly selective manner, and are thus able to block the transmission of pain very well. Consequently, these toxins are of great interest for developing analgesics for chronically ill or terminal cancer patients for whom other medications can no longer be used. "The advantage of these conotoxins is that they do not cause dependency," Imhof, a pharmaceutical chemist, explained. "Since the peptide we studied decomposes rather quickly in the body, we do, however, need more stable forms that we can administer."

Scientists replicate the rare venom in vitro

The Bonn researchers worked with Prof. Dr. Stefan H. Heinemann from the Biophysics Department of the University of Jena, scientists from the Leibniz Institute for Age Research Jena and the Technical University of Darmstadt. "The μ-PIIIA conotoxin, which was of interest in this study, occurs only in extremely minute quantities in marine cone snails," said Dr. Alesia A. Tietze, the lead author, who received her doctoral degree on Prof. Imhof's team. However, the scientists were able to produce the specific venom chemically in vitro for use in additional analyses. Tietze added, "We succeeded in identifying the structure of different μ-PIIIA conotoxin variants and their different effects using nuclear magnetic resonance."

The venom in question is a substance whose different amino acids are strung together like pearls. "This string can form clusters in different ways, forming divers 3D structures," explained Prof. Imhof. Until now it

had been thought that only one of these forms is biologically effective. "It was exactly this dogma that we were able to disprove," the Bonn scientist added. "We identified three active types of peptide folding with a similar effect – there are probably even more." These variants do, however, differ slightly with regard to their biological efficacy, representing valuable starting structures for further development into analgesics.

Consequently, the scientists want to conduct additional studies in order to find out more these different fold variants of the µ-PIIIA conotoxin. But it will take years until patients may be able to profit from this. "We are still in the basic research stadium," said Prof. Imhof.

More information: Die einzig wahre Faltung? Strukturell diverse Isomere des µ-Conotoxins PIIIA blockieren den Natriumkanal Nav1.4, (The one and only fold?...), Angewandte Chemie (DOI: 10.1002/anie.201107011).

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