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Black mamba takes away pain

By Lev Osherovich, Senior Writer

A French team has identified a pair of peptides, mambalgin-1 and mambalgin-2, from black mamba venom that could be useful for treating pain.[1] The peptides, which inhibit a class of acid-sensing ion channels on the surface of neurons, are licensed to **Theralpha S.A.S.**

Team leader Eric Lingueglia, a research director at the **Institut National de la Santé et de la Recherche Médicale** (INSERM), the Institute of Molecular and Cellular Pharmacology at **Centre National de la Recherche Scientifique** (CNRS) and the **University of Nice Sophia Antipolis**, said the analgesic peptides are nontoxic and are likely used by the snake to anesthetize its prey while other, toxic molecules do the killing.

> **"The peptide from the venom has evolved to be a very robust peptide and very stable, so it could be a drug candidate, but it's possible that there are other molecules that could block the same target."**
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> ***—Eric Lingueglia, University of Nice Sophia Antipolis***

"Venoms have been known for a long time as a source of interesting molecules, mostly toxins," he said. "These often work by blocking ion channels, which are important for neuronal excitability and other neural functions. It was also known that venoms contain other molecules such as analgesics. Mambalgins represent less than 0.5% of the total venom."

Lingueglia's team uncovered the analgesic effects of mambalgins while hunting for antagonists of acid-sensing ion channels, a family of membrane-bound proteins previously implicated in multiple neurological functions including pain and anxiety.[2]

In frog eggs transfected with rat homologs of acid-sensing ion channel-1 (Asic1) and Asic2, black mamba venom prevented activation of the channels.

The team purified the mambalgin peptides from the venom and showed that they inhibited Asic1 and Asic2 activation in several cultured mammalian cell types. The two peptides differed by only a single amino acid and behaved similarly in cell culture assays.

Because of the near-identical behavior of the peptides, the team chose one—mambalgin-1—for further study. In mice, intrathecal injections of the peptide decreased sensitivity to inflammatory pain as potently as injections of morphine.

Lingueglia suspects ASIC1 and ASIC2 may form a heterodimeric complex that is particularly sensitive to mambalgins. Previously, the two channels were thought to act as independent homodimers.

The team found that the analgesic effect of mambalgin could be mimicked by intrathecal injection of small interfering RNA that knocked down expression of *Asic2* in the CNS.

Results were published in *Nature*.

Snake juice

One big question is what signaling pathway downstream of ASIC1 and ASIC2 mediates the analgesic effect of mambalgins. Because treatment with the opioid-signaling antagonist naloxone did not fully block the analgesic effects of mambalgin injection, Lingueglia suspects the snake venom peptides work by a mechanism distinct from that for opiates.

His team is now working out the downstream effects of mambalgin signaling in a variety of mouse pain models.

Lingueglia thinks mambalgins could be a good starting point for new pain therapeutics. He noted that modeling studies of the peptides' structure suggest they are compact and stable molecules that would be well-suited for use as injectable therapeutics.

"The peptide from the venom has evolved to be a very robust peptide and very stable, so it could be a drug candidate, but it's possible that there are other molecules that could block the same target," said Lingueglia.

Lingueglia and the University of Nice Sophia Antipolis have received a patent covering the use of mambalgins for pain.

The university has licensed the patent to Theralpha, which has a formulation of mambalgin, called THA904, in preclinical pharmacokinetic and toxicology studies. The company could not be reached for comment.

Theralpha previously licensed three other analgesic compounds from the university. The study's coauthor, Michel Lazdunski, is CSO and SVP at Theralpha and a professor at the CNRS Institute of Molecular and Cellular Pharmacology at the University of Nice Sophia Antipolis.

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REFERENCES

1. Diochot, S. *et al. Nature*; published online Oct. 3, 2012; doi:10.1038/nature11494
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2. Sherwood, T.W. *et al. Am. J. Physiol. Cell Physiol.* **303**, C699–C710 (2012)

COMPANIES AND INSTITUTIONS MENTIONED

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