Mambalgins, Snake Peptides Against Inflammatory and Neuropathic Pain Through Inhibition of ASIC Channels

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Mambalgins are 57-amino acid peptides isolated from mamba venom. They produce potent analgesic effects in mice against inflammatory pain upon central intrathecal (i.t.), and peripheral local (i.pl.) injections, through inhibition of different ASICs subtypes and involvement of opioid-independent pathways. They produce fewer side effects than morphine and no apparent toxicity.

We now show that mambalgins also have an opioid-independent effect on both thermal and mechanical pain upon systemic intravenous (i.v.) administration and are effective against neuropathic pain by i.v., i.t. and i. pl. injections. By combining the use of knockdown and knockout animals, we show the critical involvement of peripheral ASIC1b-containing channels in the i.v. effects of mambalgins against inflammatory pain. The potent analgesic effect on neuropathic pain involves two different mechanisms depending on the route of administration, a naloxone-insensitive and ASIC1a-independent effect associated with i.v. injection, and an ASIC1a-dependent and partially naloxone-sensitive effect associated with i.t. injection.

We have done in collaboration with the CEA iBiTecS Institute in Gif-sur-Yvette, the full stepwise solid-phase peptide synthesis of mambalgin-1, solved its 3D crystal structure, mapped the pharmacophore, and identified the binding site and the inhibitory mechanism on ASIC1a channels.

These findings identify new roles for ASICs in pain pathways, and mambalgins as new potential analgesics against inflammatory and chronic neuropathic pain.