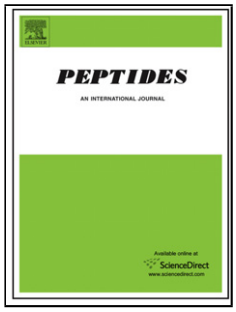

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The peptide toxin δ-hexatoxin-MrIX inhibits fast inactivation of Na_Vs in mouse cerebellar granule cells

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Highlights

- δ-hexatoxin-MrIX is a peptide toxin isolated from the venom of spider *Macrothele raveni*.
- δ-hexatoxin-MrIX inhibited the inactivation of voltage-gated sodium channels in cerebellar granule cell.
- δ-hexatoxin-MrIX could be used as a pharmacological tool to investigate the role of voltage-gated sodium channels in granule cell maturation.

Abstract

Spider venom is rich in peptide toxins that could be used to explore the structure and function of voltage-gated sodium channels (Na_Vs). This study has characterized a 44-amino acid peptide toxin, δ-hexatoxin-MrIX (δ-HXTX-MrIX), from the venom of the spider *Macrothele raveni*. δ-hexatoxin-MrIX potently inhibited the fast inactivation of Na_Vs in mouse cerebellar granule cells (CGCs) with an EC_{50} of 35.3 ± 5.9 nM. The toxin shifted both the steady-state activation and the steady-state inactivation curves of CGC Na_Vs to the hyperpolarized direction. δ-hexatoxin-MrIX also acted on $Na_V1.3$ and $Na_V1.4$ channels heterologously expressed in HEK293T cells, as well as on Na_Vs in acutely isolated cockroach DUM neurons. However, the $Na_V1.5$, $Na_V1.7$ and $Na_V1.8$ channels were resistant to δ-hexatoxin-MrIX. The toxin inhibited the fast inactivation of $Na_V1.3$ and $Na_V1.4$ with high affinity (EC_{50} values of 82.0 ± 3.0 nM and 24.0 ± 4.7 nM, respectively), but the saturating dose of toxin showed distinct efficacy on these two types of channels. δ-hexatoxin-MrIX is a peptide toxin acting on CGC Na_Vs and could be used as a pharmacological tool to explore the role of Na_Vs in granule cell maturation during cerebellum development.

Abbreviations: Na_Vs, voltage-gated sodium channels; CGC, cerebellar granule cell; DRG, dorsal root ganglia; DUM neuron, dorsal unpaired median neuron.

Keywords: δ-hexatoxin-MrIX, cerebellar granule cell, voltage-gated sodium channel