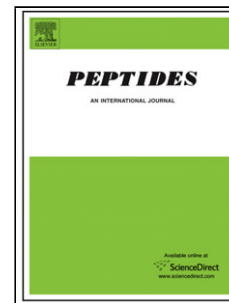


## Accepted Manuscript

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## The peptide toxin $\delta$ -hexatoxin-MrIX inhibits fast inactivation of $\text{Na}_\text{v}$ s in mouse cerebellar granule cells

Dongfang Tang\*, Zhen Xiao\*, Yan Xu\*, Jiao Zeng\*, Dezheng Peng\*, Songping Liang\*, Cheng Tang<sup>\*,1</sup>, Zhonghua Liu<sup>\*,2</sup>

\*The National and Local Joint Engineering Laboratory of Animal Peptide Drug Development, College of Life Sciences, Hunan Normal University, Changsha 410081, China.

<sup>1,2</sup>Correspondence: The National and Local Joint Engineering Laboratory of Animal Peptide Drug Development, College of Life Sciences, Hunan Normal University, Changsha 410081, Hunan, China.

Tel: +86 731 88872556; E-mail: chengtang@hunnu.edu.cn (Cheng Tang); liuzh@hunnu.edu.cn (Zhonghua Liu).

### Highlights

- $\delta$ -hexatoxin-MrIX is a peptide toxin isolated from the venom of spider *Macrothele raveni*.
- $\delta$ -hexatoxin-MrIX inhibited the inactivation of voltage-gated sodium channels in cerebellar granule cell.
- $\delta$ -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 ( $\text{Na}_\text{v}$ s). This study has characterized a 44-amino acid peptide toxin,  $\delta$ -hexatoxin-MrIX ( $\delta$ -HXTX-MrIX), from the venom of the spider *Macrothele raveni*.  $\delta$ -hexatoxin-MrIX potently inhibited the fast inactivation of  $\text{Na}_\text{v}$ s in mouse cerebellar granule cells (CGCs) with an  $\text{EC}_{50}$  of  $35.3 \pm 5.9$  nM. The toxin shifted both the steady-state activation and the steady-state inactivation curves of CGC  $\text{Na}_\text{v}$ s to the hyperpolarized direction.  $\delta$ -hexatoxin-MrIX also acted on  $\text{Na}_\text{v}1.3$  and  $\text{Na}_\text{v}1.4$  channels heterologously expressed in HEK293T cells, as well as on  $\text{Na}_\text{v}$ s in acutely isolated cockroach DUM neurons. However, the  $\text{Na}_\text{v}1.5$ ,  $\text{Na}_\text{v}1.7$  and  $\text{Na}_\text{v}1.8$  channels were resistant to  $\delta$ -hexatoxin-MrIX. The toxin inhibited the fast inactivation of  $\text{Na}_\text{v}1.3$  and  $\text{Na}_\text{v}1.4$  with high affinity ( $\text{EC}_{50}$  values of  $82.0 \pm 3.0$  nM and  $24.0 \pm 4.7$  nM, respectively), but the saturating dose of toxin showed distinct efficacy on these two types of channels.  $\delta$ -hexatoxin-MrIX is a peptide toxin acting on CGC  $\text{Na}_\text{v}$ s and could be used as a pharmacological tool to explore the role of  $\text{Na}_\text{v}$ s in granule cell maturation during cerebellum development.

Abbreviations:  $\text{Na}_\text{v}$ s, voltage-gated sodium channels; CGC, cerebellar granule cell; DRG, dorsal root ganglia; DUM neuron, dorsal unpaired median neuron.

Keywords:  $\delta$ -hexatoxin-MrIX, cerebellar granule cell, voltage-gated sodium channel

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