



HAL
open science

Multiscale functional approaches to evidence high affinity blockade of Nav1.6 channel subtype by huwentoxin-IV spider peptide

Tânia C. Gonçalves, Rachid Boukaiba, Jordi Molgó, Muriel Amar, Michel Partiseti, Denis Servent, Evelyne Benoit

► To cite this version:

Tânia C. Gonçalves, Rachid Boukaiba, Jordi Molgó, Muriel Amar, Michel Partiseti, et al.. Multiscale functional approaches to evidence high affinity blockade of Nav1.6 channel subtype by huwentoxin-IV spider peptide. 29th Ion Channel Meeting, Sep 2018, Sète, France. hal-04466966

HAL Id: hal-04466966

<https://hal.science/hal-04466966>

Submitted on 19 Feb 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

P-11 MULTISCALE FUNCTIONAL APPROACHES TO EVIDENCE HIGH AFFINITY BLOCKADE OF NAV1.6 CHANNEL SUBTYPE BY HUWENTOXIN-IV SPIDER PEPTIDE

Tânia c. GONÇALVES¹; Rachid BOUKAIBA²; Jordi MOLGO³; Muriel AMAR⁴; Michel PARTISETI²; Denis SERVENT⁴; Evelyne BENOIT³

1: Sanofi Aventis R & D, Integrated Drug discovery - In Vitro Biology & Pharmacology, F-94440 Vitry-sur-Seine, and Service d'Ingénierie Moléculaire des Protéines (SIMOPRO), CEA, Université Paris-Saclay, F-91191 Gif sur Yvette, France

2: Sanofi Aventis R & D, Integrated Drug discovery - In Vitro Biology & Pharmacology, F-94440 Vitry-sur-Seine, France

3: Service d'Ingénierie Moléculaire des Protéines (SIMOPRO), CEA, Université Paris-Saclay, F-91191 Gif sur Yvette, and Institut des Neurosciences Paris-Saclay (Neuro-PSI), UMR CNRS/Université Paris-Sud 9197, Université Paris-Saclay, F-91198 Gif

4: Service d'Ingénierie Moléculaire des Protéines (SIMOPRO), CEA, Université Paris-Saclay, F-91191 Gif sur Yvette

The Chinese bird spider huwentoxin-IV (HwTx-IV) is well-known to be a highly potent blocker of Nav1.7 subtype of voltage-gated sodium (Nav) channels, a genetically validated analgesic target, and thus promising as a potential lead molecule for the development of novel pain therapeutics. In the present study, the interaction between HwTx-IV and Nav1.6 channel subtype was investigated using multiscale (from in vivo to individual cell) functional approaches. HwTx-IV was approximately 2 times more efficient than tetrodotoxin (TTX) to inhibit the compound muscle action potential recorded from the mouse skeletal neuromuscular system in vivo, and 30 times more effective to inhibit nerve-evoked than directly-elicited muscle contractile force of isolated mouse hemidiaphragms. These results strongly suggest that the inhibition of nerve-evoked skeletal muscle functioning, produced by HwTx-IV, resulted from a toxin-induced preferential blockade of Nav1.6, compared to Nav1.4, channel subtype. This was confirmed by whole-cell automated patch-clamp experiments performed on human embryonic kidney (HEK)-293 cells overexpressing hNav1.1-1.8 channel subtypes. HwTx-IV was also approximately 850 times more efficient to inhibit TTX-sensitive than TTX-resistant sodium currents recorded from mouse dorsal root ganglia neurons. Finally, based on our data, we predict that blockade of the Nav1.6 channel subtype was involved in the in vivo toxicity of HwTx-IV, although this toxicity was more than 2 times lower than that of TTX. In conclusion, our results provide detailed information regarding the effects of HwTx-IV and allow a better understanding of the side-effect mechanisms involved in vivo and of channel subtype interactions resulting from the toxin activity.