



HAL
open science

A multiscale functional approach to assess pharmacological interactions between huwentoxin-IV spider peptide and sodium channel subtypes

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.. A multi-scale functional approach to assess pharmacological interactions between huwentoxin-IV spider peptide and sodium channel subtypes. 23th Meeting on Toxinology “ Toxins: Immunity, Inflammation and Pain ” organized by the French Society of Toxinology (SFET), Toxicon, 149, pp.105-106, 2018, 10.1016/j.toxicon.2018.02.035 . hal-02334358

HAL Id: hal-02334358

<https://hal.science/hal-02334358>

Submitted on 15 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.

A multiscale functional approach to assess pharmacological interactions between huwentoxin-IV spider peptide and sodium channel subtypes

Tânia C. GONCALVES^{1,2}, Rachid BOUKAIBA¹, Jordi MOLGÓ^{2,3}, Muriel AMAR², Michel PARTISETI¹, Denis SERVENT², Evelyne BENOIT^{2,3}

¹Sanofi Aventis R&D, Integrated Drug discovery - In Vitro Biology & Pharmacology, F-94440 Vitry-sur-Seine, France; ²Service d'Ingénierie Moléculaire des Protéines (SIMOPRO), CEA, Université Paris-Saclay, 91191 Gif-sur-Yvette, France; ³Institut des Neurosciences Paris-Saclay (Neuro-PSI), UMR 9197 CNRS/Université Paris-Sud, CNRS, 91198 Gif-sur-Yvette, France.

* Corresponding author; E-mail: Tania-Cristina.GONCALVES@cea.fr

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 approximately 90 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, it seemed obvious that blockade of 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.

Acknowledgements: This research was funded by a collaborative grant (#153114) between Sanofi-Aventis Research & Development (Chilly-Mazarin, France) and the French Alternative Energies and Atomic Energy Commission (CEA, Gif-sur-Yvette, France). T.C.G. was supported by a doctoral CIFRE fellowship from Sanofi-Aventis.

Keywords: Huwentoxin-IV, NaV channel subtypes, electrophysiology, mouse neuromuscular excitability, mouse dorsal root ganglia neurons