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Novel antinociceptive peptides interacting with sodium channels : from their identification to their multi-scale pharmacological characterization

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Abstract

Pain care is a global public health priority and current pain relievers, although effective in many cases, are too often associated with side effects. A promising approach to manage pain and avoid central side effects is to target the dorsal root ganglia (DRG) neurons, located in the periphery. These neurons are wellknown to express various proteins involved in pain transmission, including the 1.7 subtype of voltage-gated sodium channels (Na_v1.7), a major and genetically validated target for chronic pain treatment. Thanks to their high affinity and selectivity, venom peptides of animal origin have been identified as an original source of antinociceptive molecules.

The objective of my PhD is to identify and characterize, by multi-scale studies, a large number of novel antinociceptive venom peptides possessing high selectivity and potency for Na_v1.7. For this purpose, an electrophysiological screening on cells overexpressing the human Na_v1.7 allowed to identify novel hits from a unique and large venom collection of Smartox Biotechnology. The different studies, currently undertaken on some selected peptides, aim

- (1) to chemically synthesize these peptides
- (2) to characterize their selectivity profile and safety issue, notably on cell lines overexpressing Na_v subtypes (from 1.1 to 1.8) and on native systems such as the mouse cardiomyocytes and neuromuscular system,
- (3) to specify their efficiency and mechanism of action on mouse DRG neurons,
- (4) to evaluate *in vivo* their analgesic properties in vigilant mice
- (5) to determine their pharmacophore and optimize their functional properties, and
- (6) to provide evidence for the clinical potential of the best candidates in correcting *de novo* identified Na_v channelopathies.

Conclusion

Based on a collection of numerous and various venoms, this research strategy makes possible to identify and characterize different toxins of therapeutic interest in the context of their development as antinociceptive agents.

The evaluation of functional properties used here with the cyriotoxin-1a as an exemple in DRG neurons using manual *patch-clamp* and in mice *in vivo* reveals that the peptide exhibits marked antinociceptive properties, as evidenced by its effects on TTX-sensitive Na_v channels (Na_v1.7) and on tactile and heat sensitivity of animals. This allows us to consider a clinical development of the studied toxin,

Methodology and Results

