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D peptide, a promising toxin as potential antinociceptive agent targeting the Na_v1.7 subtype of voltage-gated sodium channels

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Acute pain is a physiological function associated with injury that is essential for human survival. The painful message conveys from the nociceptor activation through afferent sensitive fibers until the dorsal horn before reaching the central nervous system. This kind of pain is normally short-lasting (< 3 months). Beyond this period of time and without real injury, pathologic chronic pain is considered to result from damage in the transmission pain system itself. Pain management costs are more than \$600 billion per year in the US, far more than heart disease, cancer and diabetes [1]. Due to the lack of different therapeutic classes, the prescription of opioids remains the only option for chronic pain treatment, despite their strong side-effects on the central nervous system. Over the last two decades, animal venom toxins have been explored as an original source of new antinociceptive drugs targeting subtypes of ion channels such as ASICs, TRPs, Ca_v, K_v and Na_v channels. In particular, the Na_v1.7 subtype, expressed in afferent sensitive fibers, most particularly in dorsal root ganglia (DRG) neurons, is an antinociceptive target of choice that has been validated by human genetic evidence as congenital insensitivity to pain.

High throughput screening of Sanofi collection venom toxins, using automated patch-clamp (QPatch HT, Sophion Biosciences) on HEK cells overexpressing human Na_v subtypes, pointed out a new toxin, the D peptide, sharing the same inhibitory cysteine knot (ICK) motif with toxins reported up-to-date (e.g. ProTx-II, GpTx-I and HwTx-IV) originating from the same theraphosids spider family [2-4]. This peptide showed nanomolar range affinity for Na_v1.7, Na_v1.1, Na_v1.2 and Na_v1.3 and micromolar range affinity for Na_v1.5, Na_v1.4. Indeed, the dose-response curve of D peptide effects on Na current of HEK cells overexpressing human Na_v1.7, established using manual patch-clamp, revealed an IC₅₀ (concentration of peptide producing 50% current inhibition) of 55 nM. Moreover, in DRG neurons isolated from adult mice, the peptide preferentially inhibited with high affinity tetrodotoxin (TTX)-sensitive Na current (IC₅₀ = 170 nM), flowing through mainly Na_v1.7, compared with TTX-resistant Na current (IC₅₀ = 108 μM), flowing through Na_v1.8 and Na_v1.9. These results represent the first evidence for a potential antinociceptive agent. Finally, the D peptide had no marked *in vivo* side-effects as detected by analyzing the excitability properties of neuromuscular system in mice.

In conclusion, the pharmacological profile of D peptide is of great interest since it leads to further engineering studies aimed to optimize its potential antinociceptive use.

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