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### **P33- EVALUATION OF THE SPIDER (PHLOGIELLUS GENUS) PHLOTOXIN 1 AND SYNTHETIC VARIANTS AS ANTINOCICEPTIVE DRUG CANDIDATES**

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Over the two last decades, venom toxins have been explored as alternatives to opioids to treat chronic debilitating pain. Actually, approximately 20 potential analgesic toxins, mainly from spider venoms, are known to inhibit with high affinity the NaV1.7 subtype of voltage-gated sodium (NaV) channels, the most promising genetically validated antinociceptive target identified so far. The present study aimed to consolidate the development of phlotoxin 1 (PhITx1), a 34-amino acid and 3-disulfide bridge peptide of a Phlogiellus genus spider, as an antinociceptive agent by improving its affinity and selectivity for the human (h) NaV1.7 subtype. The synthetic homologue of PhITx1 was generated and, as the natural peptide, equilibrated between two active forms on reverse-phase liquid chromatography and exhibited potent analgesic effects in a mouse model of inflammatory pain. The effects of PhITx1 and 8 successfully synthesized alanine-substituted variants were studied (by automated whole-cell patch-clamp electrophysiology) on cell lines stably overexpressing hNaV subtypes, as well as two cardiac targets, the hCaV1.2 and hKV11.1 subtypes of voltage-gated calcium (CaV) and potassium (KV) channels, respectively. PhITx1 and D7A-PhITx1 were shown to inhibit hNaV1.1-1.3 and 1.5-1.7 subtypes at hundred nanomolar concentrations, while their affinities for hNaV1.4 and 1.8, hCaV1.2 and hKV11.1 subtypes were over micromolar concentrations. Despite similar analgesic effects in the mouse model of inflammatory pain and selectivity profiles, the affinity of D7A-PhITx1 for the NaV1.7 subtype was at least 5 times higher than that of the wild-type peptide. Computational modelling was performed to deduce the 3D-structure of PhITx1 and to suggest the amino acids involved in the efficiency of the molecule. In conclusion, the present structure-activity relationship study of PhITx1 results in a low improved affinity of the molecule for the NaV1.7 subtype but without any marked change in the molecule selectivity against the other studied ion channel subtypes. Further experiments are therefore necessary before considering the development of PhITx1 or synthetic variants as antinociceptive drug candidates.