The Analgesic Effect of α9/10 Toxins Does Not Involve Activation of GABA<sub>B</sub> Receptors

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Introduction: Nociception is highly regulated by the activity of voltage-gated and ligand-gated ion channels. Thus, there is great interest in developing novel pain management therapies that target these channels. One class of ion channel blockers that target α9/10 nicotinic acetylcholine channel/receptors (nAChR) has been shown in animal models to have analgesic properties, but the mechanism may involve inhibition of voltage-gated calcium (Ca<sub>V</sub>) channels via activation of G protein-coupled GABA<sub>B</sub> receptors. In collaboration with researchers at the University of Utah, we tested toxins targeting α9/10 nAChR to assess their effect on Ca<sub>V</sub> current in rat sensory neurons.

Methods: Ca<sub>V</sub> currents were recorded from dorsal root ganglion neurons isolated from Sprague Dawley rats. The modulation of this current was tested using the GABA<sub>B</sub> receptor agonist baclofen (30 µM) to ensure the expression of these receptors in the recorded neurons and 1 µM each of the following the α9/10 toxins K14J14, K14J12, RglA, and Vc1.1. All of these toxins were isolated from cone snails.

Results and Discussion: Baclofen inhibited Ca<sub>V</sub> current in all neurons tested, which verified the expression of GABA<sub>B</sub> receptors. However, there was no significant effect on this current by any of the α9/10 nAChR toxins. While the K14J14 and K14K12 toxins had not been previously tested on Ca<sub>V</sub> current, several publications from one lab had demonstrated Ca<sub>V</sub> current inhibition by RglA and Vc1.1. It is not clear why our results differ, but the toxin concentration that we used was ~10x higher than that used previously. This, along with the baclofen-induced inhibition, suggests that an effect on Ca<sub>V</sub> currents would have been observed if these toxins were indeed activators of GABA<sub>B</sub> receptors.

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