Species difference in α-conotoxin RegIIA inhibition of neuronal nicotinic acetylcholine receptors: molecular basis for differential sensitivity

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Nicotinic acetylcholine receptors (nAChR) play important roles in various physiological and pathophysiological conditions including pain, anxiety, fatigue, memory and learning. Selective α3β4 nAChR antagonists are invaluable for evaluating the functional roles of this subtype in various conditions, including lung cancer and nicotine addiction. A new α4/7-conotoxin RegIIA, isolated from *Conus regius*, inhibits acetylcholine (ACh)-evoked currents mediated by rat α3β2, α3β4, α6-containing and human α7 nAChR subtypes (Franco *et al*., 2012). However, an increasing literature on the pharmacological difference between rat and human nAChR is emerging. RegIIA, when tested on human α3β2 subtype expressed in *Xenopus* oocytes, exhibited a 700-fold decrease in potency compared to rat α3β2 nAChR. However, no change in half-maximal inhibition (IC_{50}) by RegIIA was observed at the human α3β4 nAChR subtype. Site-directed mutagenesis of the ACh binding pocket residues of rat α3β2 nAChR to its corresponding human subtype revealed a crucial residue change at rat α3[Q223P] contributed significantly to the inter-species pharmacological difference. Interestingly, this single residue change caused 520-fold lower potency whereas all other residue mutations resulted in only a 2-3 fold change. Molecular dynamics simulations of RegIIA bound to the ACh binding pocket extended our understanding of RegIIA interactions with α3β2 and α3β4 nAChR subtypes and elucidated the key residues involved in the receptor binding site. Furthermore, we have obtained valuable information for the future design and development of α3β4-selective drugs that could target lung cancer and nicotine addiction.

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