Área: MED

Computational Analysis of the Molecular Interaction between Muscarinic Acetylcholine Receptor M2 and *Tityus Serrulatus* scorpion toxin Ts3.

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Highlights

This research aims to study and develop the modeling interaction between Ts3 toxin and muscarinic M2 receptor, intending to explore an alternative treatment for effects of *Tityus serrulatus* venom.

Resumo/Abstract

Scorpionism is classified as a neglected tropical disease by the World Health Organization (WHO), disproportionately affecting marginalized areas. In Brazil, *Tityus serrulatus* is responsible for the majority of scorpion-related accidents, with acute pulmonary edema being the primary cause of death in severe cases. The conventional treatment relies on antiscorpion serum, which presents significant storage and distribution challenges, limiting accessibility in remote communities. Consequently, the development of novel therapeutic strategies capable of mitigating envenomation effects before serum administration is of great pharmacological interest. Hypertension is a critical *Tityus serrulatus* bite complication and identifying venom-derived peptides with hypotensive properties could provide prophylactic benefits for envenomed patients. The muscarinic M2 receptor (M2R), a G-protein-coupled receptor (GPCR), plays a key role in cardiovascular regulation by modulating heart rate and blood pressure through parasympathetic signaling, and evidence suggests that venom toxins, such as Ts3, may interact with cardiac regulatory pathways, potentially activating the M2R. Thus, Ts3-mediated M2R activation could serve as a mechanism to counteract hypertension induced by envenomation. Therefore, this study explores the potential of the Ts3 toxin, a component of *Tityus serrulatus* venom, as an agonist of the acetylcholine M2R. To investigate this, molecular modeling and computational simulations were employed to characterize the interaction between Ts3 (PDB ID: 5CY0) and the M2 receptor (PDB ID: 7T8X). The method was validated by cross-docking using a protein complex of the receptor with acetylcholine (PDB ID: 7T8X), its natural agonist, and with iperoxo (PDB ID: 4MQS), a powerful M2R agonist. The cross-docking was performed on a restricted binding site, focusing on key amino acids involved in M2 receptor activation. Validation resulted in 2.6176 Å RMSD, comparing ligands, and an energy score of -150.09. Docking studies through HDOCK server assessed the interaction between M2R and the toxin. With that, two optimal complexes were selected, yielding in energy scores of -92.79 and -71.30. Future research steps will involve molecular dynamics simulations to evaluate the structural stability of the toxin–M2 receptor complex and clarify at a molecular level, how this interaction occurs.

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