Área: MED

Computational modeling of bradykinin (BK) potentiation by the Ts14 toxin, present in the venom of the scorpion *Tityus serrulatus.*

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Keywords: *Tityus serrulatus, Neglected Tropical Diseases, Bradykinin, Hipotensive Toxin.*

Highlights

This research aims to study and develop the modeling interaction between Ts14 toxin and bradykinin B2 receptor, intending to explore an alternative treatment for some effects of *Tityus serrulatus* venom.

Abstract

Neglected tropical diseases (NTDs), according to the WHO (World Health Organization) classification, are endemic illnesses that persist in the most economically disadvantaged and marginalized populations in tropical countries. In this context, accidents caused by venomous animals and, in particular, scorpions, with their venoms made up of complex biochemical mixtures, are included. In Brazil, *Tityus serrulatus*, known as the yellow scorpion, is responsible for the majority of accidents, the most serious of which can cause pulmonary edema or cardiogenic shock. The prophylaxis used in these cases is the use of anti-scorpion serum (ASS), which, however, is a drug that is difficult to manufacture and maintain, with very specific temperature conditions. Thus, the possibility of evaluating new drugs that can precede the serum, inhibiting one or more effects of the scorpion accident, is of great pharmacological interest. Protein-protein interactions (PPIs) basically control all intra- and extra-cellular processes in living beings. In the case of scorpions, the focus is on ligand-receptor interactions. Considering the problem of hypertension as an effect of the animal's venom, the existence of a protein with a hypotensive function could have a prophylactic effect on the patient. In this sense, this work studies the Ts14 toxin (also known as TsHpt-I), a hypotensin present in the venom of *Tityus serrulatus*, with the aim of modeling the mechanism of action of bradykinin potentiation and evaluating the possibility of making it a prophylactic drug. Firstly, as there were no crystallized structures of the toxin, using AlphaFold 2.0, a model was developed and, understanding its agonist mechanism, the biochemical target was then aimed at. Using the crystal of the BK complex with the B2 (or B2R) receptor (PDB code: 7F6H), the interactions were demarcated for the validation phase of the docking methodology and platform. On the HPEPDock server, using a hybrid approach combining rigid and flexible coupling methods to predict interactions between proteins and peptide ligands, redocking was used, based on the energy minimization of the BK obtained from the mentioned crystal (RMSD: 0.695A and an energy score: -206.305) and a crossdocking with another crystal from the BK-B2R complex (PDB code: 7F2O) (RMSD: 0.503 and energy score: -361.74), varying the number of runs and the number of amino acids known as responsible for receptor activity. Then, docking was carried out between Ts14 and B2R, focusing on the C-terminal portion, which contains the proline doublet (main similarity with BK), finding poses correlated with the action of the agonist (energy scores around -143.843). For the next steps, molecular dynamics of the complex and the membrane receptor will be carried out, to evaluate the stability of this conformation.

Acknowledgments

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