Área: MED

A molecular modeling study on the interaction between bradykinin B2 receptor (B2R) and scorpion Ts14 toxin.

Gustavo C. Ferraz (IC), [1]* Ana P. Contelli (IC), [1] Wítor R. Ferraz (PG), [2] André B. Penteado (PG), [2] Eliane C. Pedrozo (PQ), [1] Gustavo H. G. Trossini (PQ). [2]

gugascabral@usp.br

[1]Department of Chemical Engineering, Lorena School of Engineering – EEL/USP;
[2]Faculty of Pharmaceutical Sciences, University of São Paulo (FCF-USP).

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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 effects of *Tityus serrulatus* venom.

Abstract

According to the WHO (World Health Organization) classification, neglected tropical diseases (NTDs) are endemic illnesses that persist in the most economically disadvantaged and marginalized populations in tropical countries which covers accidents caused by venomous animals and, particularly, scorpions. In Brazil, *Tityus serrulatus*, the yellow scorpion, is responsible for the majority of envenomation cases, which can lead to severe complications such as pulmonary edema and cardiogenic shock. The primary treatment, anti-scorpion serum (ASS), faces challenges in production and storage due to stringent temperature requirements, underscoring the need for alternative prophylactic drugs to mitigate venom effects. In parallel, protein-protein interactions (PPIs) regulate intra- and extracellular processes, and in scorpion envenomation, ligand-receptor interactions are critical. Given that hypertension is a key effect of scorpion venom, identifying proteins with hypotensive properties could offer prophylactic solutions. In this sense, this work studies the Ts14 toxin (also known as TsHpt-I), a 24 amino acid hypotensive peptide present in the venom of *Tityus serrulatus*, aiming to model its bradykinin (BK) potentiation mechanism and evaluate its potential as a prophylactic drug. Firstly, AlphaFold 2.0 was used to constructed the target model and elucidate its agonist mechanism, providing insights for further analysis. The BK-B2 receptor (B2R) crystal structure (PDB code: 7F6H) was used for docking methodology validation. Redocking on HPEPDock and HDock servers, with energy minimization of BK from the crystal structure, yielded precise results (respectively, RMSD 0.695 Å, energy score -206.305 and RMSD 0.503 Å, energy score 394,740). 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 agonist-like poses (for HPEPDock, RMSD: 0.091 Å with an energy score of -143.445 and, for HDock, RMSD: 0.295 Å with an energy score of -281.77). Next, a molecular dynamics simulation was carried out on GROMACS 2024.2. An AMBER03 force field was used, in a 1.2 nm buffered cubic box, with the 8 C-terminal amino acids of Ts14. Average temperature obtained was 309.8 K on a neutral pH. The analysis assessed the molecule's trajectory over a 10000 ps simulation. Thus, we managed to identify stability at the temperatures tested for this portion of 8 C-terminal amino acids, a characteristic also mimicked by the portion of 4 C-terminal amino acid of Ts14.

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