Área: MED

Interaction between the scorpion toxins Ts3/Ts10 and Angiotensin Converting Enzyme 1: a computational analysis.

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Highlights

This work uses molecular modeling tools to investigate the interaction between Ts3 and Ts10 toxins, derived from the venom of the scorpion *Tityus serrulatus*, and Angiotensin Converting Enzyme 1.

Resumo/Abstract

Neglected tropical diseases persist in poor and marginalized areas, affecting more than a sixth of the world's population, and accidents involving venomous animals are included in this category. In Brazil, the scorpion *Tityus serrulatus* accounts for the majority of these accidents. Although most cases receive treatment within three hours, a significant percentage (around 10%) of cases are delayed, which can result in severe complications and death. Conventional anti-scorpion serum is produced from the plasma of horses hyperimmunized with *Tityus serrulatus* venom, but it requires specific storage and transport conditions, which makes it expensive, leads to uneven distribution of the drug, and limits access for small and riverside communities. Thus, there is a pressing need for alternative treatments to conventional antiscorpion serum, which can reduce production and distribution costs, expanding access to treatment. The angiotensin-converting enzyme (ACE 1) is associated with clinical manifestations of arrhythmia, respiratory and cardiac failure, shock, and hypertension caused by *Tityus serrulatus* venom. Targeting this enzyme requires studying inhibitors to interrupt its effects. While there are conflicting findings from other researchers regarding the function of the Ts3 and Ts10 toxins from scorpion venom, this study aimed to clarify how these toxins interact with ACE 1 at a molecular level, if such interaction occurs. Ts10 is a peptide consisting of 13 amino acids, 12 of which are repeated from the first 10 amino acids of the N-terminal portion of Ts3, which is composed of 64 amino acids in total. Initially, Ts3 was modeled using Alphafold, followed by protein-peptide docking using HPEPDOCK 2.0. Since there is no crystal structure of the Ts3 and Ts10 complex with ACE 1, a control complex between ACE 1 and a natural peptide inhibitor from the venom of the snake *Gloydius blomhoffii* (PDB code: 4APJ) was chosen. The method was validated through cross-docking (RMSD: 0.414, energy score: -109.772) and re-docking (RMSD: 0.434, energy score: -117.036). It involved 35 runs with a limited number of amino acids known to be crucial for ACE inhibition, thereby restricting the size of the interaction box. Subsequently, docking between ACE 1 and the first four amino acids of the toxins' N-terminal portion resulted in an energy score of -112.077. For the preliminary molecular dynamics simulation using GROMACS, the movement of the peptide in a neutral pH solution at a temperature of 309 K was analyzed for 30 ns. The force field chosen was AMBER03, and a 1.2 nm buffer was used between the edge of the cubic box and the outside of the peptide. Subsequently, to check for the formation of secondary structures, the previous procedure was repeated for the four amino acids of the N-terminal portion of the toxins.The analysis of the molecular dynamics results involved evaluating the generated trajectory and checking the parameters through graphs: radius of gyration, RMSD variation over time, and residue fluctuation. The results suggest that the probability of interaction is indeed higher for these four residues, and no secondary structure formation was observed.

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