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MOLECULAR DYNAMICS ANALYSIS OF THE Na⁺- TAUROCHOLATE COTRANSPORTING POLYPEPTIDE (NTCP) IN COMPLEX WITH THE ANTIVIRAL DRUG BULEVIRTIDE

Background. Bulevirtide (BLV) is the only drug approved by the European Medicines Agency and the Food and Drug Administration for the treatment of chronic hepatitis D, a severe liver disease caused by hepatitis D virus (HDV) infection in individuals infected with hepatitis B virus (HBV). BLV is an entry inhibitor that competitively binds to the Na⁺-taurocholate cotransporting polypeptide (NTCP), the cellular receptor used by both HDV and HBV for hepatocyte entry [1–2]. **Methods.** Molecular dynamics simulations of NTCP with and without BLV were performed using the 8RQF structure [2] in GRO-MACS 2023.3 [3] with the CHARMM36m force field [4] for 300 ns, followed by comparative structural and dynamic analyses. **Results.** Because BLV is an N-myristoylated lipopeptide, the topology parameters for the N-terminal N-tetradecanoylglycine residue compatible with the CHARMM36m force field were developed, enabling simulation of the complete BLV-NTCP complex. BLV binding did not substantially alter NTCP compactness, as indicated by similar radius of gyration and solvent-accessible surface area values in the bound and unbound states. However, the principal component and free energy landscape analyses revealed distinct predominant conformational states of free and BLV-bound NTCP. Throughout the simulation, BLV formed a mean of 13.7 ± 3.0 hydrogen bonds with NTCP, while the mean binding free energy of the BLV-NTCP complex was -186.9 ± 24.5 kcal/mol, indicating a highly stable protein-ligand complex. **Conclusions.** These findings provide molecular-level support for the mechanism underlying BLV-mediated inhibition of HDV and HBV entry and highlight NTCP as a promising target for the development of additional competitive entry inhibitors.

Keywords: bulevirtide, NTCP, hepatitis D virus, hepatitis B virus, molecular dynamics, entry inhibitor, topology, binding free energy.

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