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Molecular dynamics simulation of propofol bound to human serum albumin using linear interaction energy method

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Background and Aims: Human serum albumin (HSA) is one of the most abundant proteins in the circulatory system and plays a crucial role in the transport of different drugs, metabolites, and fatty acids. Therefore, a drug binding to serum albumin is an important parameter to determine pharmacokinetic and pharmacodynamics properties for chemical substances in the human body. However, despite the numerous attempts to characterize the HSA binding sites involved in this process, none of them have employed linear interaction energy method to predict binding affinities and compare them to the experimentally determined ones. Here, we performed classical molecular dynamics (MD) simulations on general anesthetic propofol bound to HSA to describe the drug binding affinity using linear interaction energy method.

Method: Molecular mechanics potential energy minimization and MD simulations were carried out using the program package GROMACS v.4.5.5. The position restrained run was performed for 1.0 ns of NVT (constant volume and temperature) ensemble dynamics to relax the water while applying restraints to the protein and equilibrate the system. The production run was then performed at constant pressure and temperature (NPT) for 1.0 ns for ligand and 15 ns for complex and at 300 K. The Particle-Mesh-Ewald (PME) method was used to treat long-range Coulombic interactions. The LINCS algorithm was used to constrain bond lengths involving hydrogen's, permitting a time step of 2 fs. Van der Waals force and Coulomb interactions were maintained at 1.0 nm according to Kerrigan's protocol. The trajectory files were analysed through the g_energy, g_sas, g_dist, and g_lie GROMACS utilities in order to compute the appropriate functions. The g_lie program used the LIE equation as: $\Delta Gbind = \alpha(<V_{l\text{-}s\ LJ}>p - <V_{l\text{-}s\ LJ}>w) + \beta(<V_{l\text{-}s\ el}>p - <V_{l\text{-}s\ el}>w)$, where the $<V_{l\text{-}s\ LJ}>p$, $<V_{l\text{-}s\ LJ}>w$, $<V_{l\text{-}s\ el}>p$, and $<V_{l\text{-}s\ el}>w$ parameters are Lennard-Jones and electrostatic terms for ligand/protein or ligand/water interactions with scaling factors (α, β).

Results: Fifteen-nanosecond molecular dynamics simulations were performed on propofol bound to human serum albumin as a result of this drug pharmacokinetic distribution in the circulatory system. The linear interaction energy method was implemented to explore the propofol binding affinity (Kd) for its different binding sites (PR1 and PR2) of HSA. MD simulations indicate that HSA-ligand interactions are dominated by hydrophobic force for PR1 and hydrogen-bonding for PR2. The letter site was detected to establish strongest binding for propofol with ΔG_{bind} = -23.804 kJ*mol^{-1} and Kd_{pred}=62.68 μM (Kd_{exp}=65μM) while PR2 only provided ΔG_{bind} = -20.41 kJ*mol-1and Kd_{pred} of 249.11 μM, respectively. Our findings also indicate that the PR2 binding cavity is less shallow with more considerable flexibility for the ligand than PR1 due to a higher buried surface area (BSA) and HSA-propofol distance variations.

Conclusion: This study illustrates that molecular dynamics can provide a useful and accurate picture of protein-ligand interaction at the molecular level. This could be achieved because MD simulations mimic certain key physiological conditions, such as temperature, ion content, solvation, etc. Overall, this study provides the evidence of different binding affinities for different HSA binding sites that might help to explain the high ligand promiscuity of HSA

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