COMPUTATIONAL STUDIES OF HUNTINGTIN PROTEIN: CLASSIFICATION & BINDING PATTERN DETERMINATION

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INTRODUCTION AND RESEARCH AIM

Huntington's disease (HD) is a neurodegenerative disorder characterized by progressive motor disability, psychiatric abnormalities, and cognitive dysfunction in individuals who carry a mutant allele. To understand the molecular basis of its dysfunctions, computational studies have been employed to explore the mechanisms of HD. We have previously studied the binding of small molecules with HD protein, HIP14. The objective of this study was to develop computational methods to understand the binding of small molecules with HIP14.

EXPERIMENTAL DETAILS

Ligands were docked using Autodock4.10 and classified using the WEKA suite. Molecular dynamics simulations were performed using Gromacs 5281021. The crystal structures of HIP14 and targets were obtained from the PDB.

RESULTS

The root-mean-squared deviation (RMSD) of the docked conformers was calculated to be 1.522 Å. The potential energy of the docked conformers was found to be stable, with a difference of 6.77 kcal/mol. The classification results showed that the WEKA suite could classify the ligands with an accuracy of 80.924%.

DISCUSSION

Based on experimental data, molecular docking and dynamics study were performed to explore the inhibition mechanism of 42 inhibitors toward HIP14. Our results suggested that molecule 5281021 can easily bind to the active pocket of HIP14 to display inhibition. The binding mode may alter with the changing of some substituents on protein positions. The inhibitors with dimethyl amine substituted as such as in 5281021a and 5281023 molecule bind to HIP14 with a ASP122. In other cases, inhibitors substituted with fluoro-sulfonamide anchored to the active pocket. The ligand orientation in the active site can greatly affect the stability of the ligand-receptor complex; moreover, only conformations with aromatic backbones buried in the hydrophobic special pocket are dynamically stable. Our molecular dynamics simulation of the HIP14:5281023 complex reveals favorable dynamics as shown by the RMSD plots (graph 1, 3 and 5). The complex show stable dynamics in 500ps simulation. Our simulation results give almost similar dynamics of protein backbone suggesting stability of crystal structure of HIP14:5281023. The HIP14:5281023 complex generated by docking shows relative stability in MD simulation, and confirms consistency of HIP14:5281023. With proper modification, the fluoro-sulfonamide binding mode can completely eliminate the pKa effect of carboxyl or hydroxyl groups, and could be a new kind of promising HIP14 inhibitor.

REFERENCES