World Academy of Science, Engineering and Technology
International Journal of Chemical and Molecular Engineering
Vol:18, No:06, 2024

Insights Into Serotonin-Receptor Binding and Stability via Molecular Dynamics Simulations: Key Residues for Electrostatic Interactions and Signal Transduction

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Abstract : Serotonin-receptor binding plays a key role in several neurological and biological processes, including mood, sleep, hunger, cognition, learning, and memory. In this article, we performed molecular dynamics simulation to examine the key residues that play an essential role in the binding of serotonin to the G-protein-coupled 5-HT_{1^B} receptor (5-HT_{1^B} R) via electrostatic interactions. An end-point free energy calculation method (MM-PBSA) determines the stability of the 5-HT1B R due to serotonin binding. The single-point mutation of the polar or charged amino acid residues (Asp129, Thr134) on the binding sites and the calculation of binding free energy validate the importance of these residues in the stability of the serotonin-receptor complex. Principal component analysis indicates the serotonin-bound 5-HT1BR is more stabilized than the apo-receptor in terms of dynamical changes. The difference dynamic cross-correlations map shows the correlation between the transmembrane and mini-Go, which indicates signal transduction happening between mini-Go and the receptor. Allosteric communication reveals the key nodes for signal transduction in 5-HT1BR. These results provide useful insights into the signal transduction pathways and mutagenesis study to regulate the functionality of the complex. The developed protocols can be applied to study local non-covalent interactions and long-range allosteric communications in any protein-ligand system for computer-aided drug design.

Keywords : allostery, CADD, MD simulations, MM-PBSA
Conference Title : ICTACC 2024 : International Conference on Theory and Applications of Computational Chemistry
Conference Location : Paris, France
Conference Dates : June 20-21, 2024