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GPCR Surface Facilitates Membrane Crossing of Drug Molecules and Lipids: A Martini 3 Study

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G protein-coupled receptors (GPCRs) play a crucial role in modulating physiological responses by transmitting extracellular signals into the cell. Moreover, they are the main target of drugs like salmeterol and salbutamol, which act against pulmonary diseases by activating the GPCR, β2-adrenergic receptor (β2AR). In this study, we employ coarse-grained molecular dynamics simulations with the Martini 3 force field to investigate the behavior of these drugs and phospholipids in the presence of β2AR. Our results reveal that both drugs and lipids exploit the protein surface to traverse the membrane and change leaflets (flip-flop). During unbiased trajectories, 50% to 70% of the drug flip-flops occur on the β2AR surface, while lipids exclusively flip-flop on β2AR. We analyzed the primary drug flip-flop path on the β2AR surface and conducted umbrella sampling calculations along spontaneous flip-flop pathways. The resulting energy barriers for the permeation of both drugs drop by more than 15 kJ/mol, and the flip-flop rate constant increases by three orders of magnitude on β2AR. Our findings provide valuable insights into the membrane permeation mechanisms and interactions of drugs and lipid flip-flops. They contribute to comprehending GPCR dynamics, the most abundant class of transmembrane proteins in the human body. Beyond this, these results could benefit strategies for designing drugs necessitating efficient cell permeation as we validated with two different kinase inhibitors.

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