Molecular determinants for binding and function at serotonin 5-HT_{2A} and 5-HT_{2C} GPCRs: Ligand Docking, Molecular Dynamic and Quantum Mechanic Studies

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The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) mediates some of its diverse physiological and psychological effects by activation of the 5-HT_2 family of G protein-coupled receptors (GPCRs) that consists of the 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} subtypes. Activation of the human 5-HT_{2C} receptor is therapeutic for obesity and 5HT_{2C} agonists are under development for neuropsychiatric disorders. In contrast, activation of 5-HT_{2A} and 5-HT_{2B} receptors is associated with hallucinogenic and adverse cardiopulmonary effects, respectively. Drug discovery targeting the 5-HT_{2C} receptor is challenging because it shares about 75% transmembrane sequence identity and same second messenger signaling with 5-HT_{2A} and 5-HT_{2B} receptors. Moreover, there are no 3D crystal structures for any of the 5-HT_2 GPCRs. Here, 5-HT_{2A} and 5-HT_{2C} homology models were built from the β_2-adrenergic GPCR crystal structure. Docking studies were carried on the model receptors for our candidate drug ligands including (–)-*trans*-p-Cl-PAT (1*R*, 3*S*-(–)-*trans*-[*para*-chloro]-1-phenyl-3-*N*,*N*-dimethylaminotetralin) and reference ligands. Selected docking poses were subjected to molecular dynamics simulations with the receptor embedded in a palmitoyloleoyl phosphatidylcholine bilayer. Binding pocket models of the ligands docked at the active sites were derived from the optimal poses of the ligands at 5-HT_{2A} and 5-HT_{2C} receptors, and used in quantum mechanics calculations using DFT method B3LYP/6-31G(d,p). Highlights of specific ligand–receptor interactions of p-Cl-PAT involve residues M6.47, W6.48, F6.51, V7.39, G7.42, Y7.43, at 5-HT_{2C}. Molecular interactions are discussed toward delineating the molecular determinants underlying differential activation of 5-HT_2 GPCRs.

Keywords: Serotonin 5-HT_{2A}, 5-HT_{2C}, GPCR, ligand-receptor interactions, homology modeling, docking, molecular dynamics, POPC bilayer, DFT calculations, drug design