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The Mechanism of Ligand Binding to CB1 Cannabinoid Receptor

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Although most ligands enter G-protein-coupled receptors (GPCRs) from extracellular site, it has been reported, that some hydrophobic ligands access the receptor's binding site from the membrane rather than from bulk water. In order to identify the most probable ligand entrance pathway into CB1 receptor orthosteric binding site we performed several Steered Molecular Dynamics (SMD) simulations of various CB1 ligands, pulling them from the receptor's binding site with constant velocity and the smallest forces were measured during pulling between TM7-TM1/TM2 helices. We have also performed Supervised Molecular Dynamics (SuMD) simulations for two CB1 agonists, an and amide and THC, entering CB1 receptor's binding site and found the same pathway as in pulling simulations. Using SuMD we were also able to reproduce the THC binding pose predicted by docking to CB1 receptor crystal structure [1]. The results of similar simulations performed for S1P1 receptor, together with the mutagenesis studies results for rhodopsin [2] suggest that the ligand entrance between TM7 and TM1 is a quite common scenario for hydrophobic ligands binding GPCR's.

Biography:

Jakub Jakowiecki graduated from a high school with natural profile. Afterwards he studied at the Interfaculty Individual Studies in Mathematics and Natural Sciences (MISMaP) at University of Warsaw. In 2008 he received his Masters degree in Chemistry (specialization: organic chemistry) and started his PhD studies in organic chemistry at University of Missouri (Columbia, Missouri in United States) which he has not finished because of health problems. In 2013 Jakub changed his specialization to theoretical chemistry and started a PhD research in biomodeling group directed by prof. Sławomir Filipek at the University of Warsaw. He has been studying Gprotein coupled receptors (GPCRs) and other membrane proteins ever since. His scientific interests focus on GPCRs binding hydrophobic ligands, especially cannabinoid and sphingosine1phopshate receptors, which are the topic of his PhD thesis. He also works in the project which aims to find a cure for Alzheimer's disease and participates in a development of GPCRM modeling service (a non-profit web service for GPCRs modeling). In his research Jakub uses techniques such as: Homology modeling, *ab initio* modeling, docking, interaction fingerprints (IFPs) and molecular dynamics simulations (MD) plus various modifications of this method, such as steered molecular dynamics (SMD), supervised molecular dynamics (SuMD) and replica exchange molecular dynamics (REMD).