Insilico Study of the $A_{2A}R$-D_2R Kinetics and Revelation of Residues Involved at the Interfacial Surface for Heteromerization

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The structural and dynamic information of $A_{2A}R$-D_2R could provide a more complete understanding of the molecular and energetic basis of GPCR oligomerization, thus facilitating the design of novel GPCR oligomer-specific drugs. The biochemical and functional study suggested the $A_{2A}R$–D_2R interactions may provide new therapeutic target for Parkinson's disease. In the present work, the analysis of structure-based features (e.g., Alpha, Beta, SurfAlpha, and SurfBeta; GapIndex, Leakiness and Gap Volume) with implementation of slow mode analysis (ENM) facilitated the prediction of kinetics (K_{off}, K_{on}, and K_d) of $A_{2A}R$-D_2R protein-protein interaction. Kinetic constant of $A_{2A}R$–D_2R has been predicted to address the association-dissociation of $A_{2A}R$-D_2R complex using slow mode elastic network model showed correlation coefficient of K_d and K_{on} was 0.294 and the correlation coefficient of K_d and K_{off} was 0.635 describe stable interfacial contact of dimmer. The results demonstrated the stable hetromerization (association; Kslow) between the A2AR and D_2R, and presumed that interfaces contacts depended on the coulombic interaction between the D_2R intracellular loops (ICLs) and C-terminal tails of the A2AR. Structural dynamic properties study, ENM and KFC server based hot-spot analysis illustrated the stoichiometry of ($A_{2A}R$-D_2R) contact interfaces as dimmer. The propensity of surface amino acid involved in interaction illustrated the presence of positively (Arg, R; His, H; and Lys,K) and negatively (Glu, E) and Asp, D) charged structural motif of TMs and ICL3 of $A_{2A}R$ and D_2R with significant columbic forces at interface of dimmer contact crystal structure.