An improved model of class C GPCR family member sweet taste receptor : construction and dynamics

Elaheh Kashani-Amin[a], Amirhossein Sakhteman*[b,c], Bagher Larijani[d], Azadeh Ebrahim-Habibi*[a]

[a]Biosensor Research Center, Endocrinology and Metabolism Molecular-Cellular Sciences Institute, Tehran University of Medical Sciences

[b] Department of Medicinal Chemistry, School of Pharmacy, Shiraz University of Medical Sciences

[c]Medicinal Chemistry and Natural Products Research Center, Shiraz University of Medical Sciences

[d]Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

* Corresponding authors: aehabibi@sina.tums.ac.ir, asakhteman@sums.ac.ir

Abstract: Sweet taste receptor, a heterodimer of T1R2 and T1R3 molecules, has not yet been experimentally observed. Molecular modeling techniques play a critical role in understanding atomic details of ligand binding or mechanism of action as a single receptor for various chemical structures. In recent years, several models of the individual domains or whole structure of the receptor have been provided. In this study, an enhanced model of sweet taste receptor is introduced. VFTM, CR and TMD were constructed separately. Quality of each model was evaluated by 60 ns of MD simulation in three iterations. Details of dynamics, secondary structure changes and orthosteric ligand binding site characteristics were investigated via interactions with experimentally known ligands, e.g. aspartame, or analysis of the reported key residues during simulation time. We showed that individually construction of the VFTM and CR domains improves quality of the model. However, further formation of a conserved disulfide bond between two distant cysteines in VFTM and CR domains affects structural dynamics and secondary structure in both monomers. These effects were discussed by 50 ns simulation in two iterations for both T1R2 and T1R3. We also showed that this bond has no significant effect on compactness of the orthosteric binding pockets.

Key words: Sweet Taste Receptor; T1R2; T1R3; C GPCR; Homology Modeling; Ligand Docking