Scrose-driven effects on structure-function relationships in human sweet taste receptor

SUCROSE-DRIVEN EFFECTS ON STRUCTURE-FUNCTION RELATIONSHIPS IN HUMAN SWEET TASTE RECEPTOR

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Introduction

Human sweet taste receptor is a TAS1R2 and TAS1R3 heterodimer belonging to the C family of GPCR. Each monomer comprises different structural domains, including the transmembrane domain (TMD), a cysteine-rich domain (CRD) and a large extracellular N-terminus (VFTM). This receptor responds to many compounds, e.g. natural sugars, that dock into the orthosteric site in the VFTM. Despite its crucial role in sweet taste prediction, the molecular activation mechanism is still unclear. The most accredited hypothesis for class C GPCR is that after ligand binding into the VFTM the receptor undergoes through a series of conformational changes evolving from the resting state, where the VFTM domains are both in the *open* configuration, to the active conformation, where at least one VFTM is in the *closed* conformation [1]. The transition in the VFTM module propagates up to the transmembrane module, that activates the coupled G protein on the intracellular side [2]. Molecular modelling, thanks to a detailed atomistic resolution, provides tools to characterize the physical and mechanical properties of proteins, and their variations arising after ligand binding. In this work, molecular dynamics (MD) simulations on human sweet receptor underline the sucrose-induced effects on the protein conformational properties. The final aim is to shed light on the molecular mechanism of action of sugars affecting the sweet receptor structure-function relationship, that drives taste perception.

Methods

The 3D atomic structure of the human sweet taste receptor was built by homology modelling starting from a similar class C GPCR, namely the metabotropic glutamate receptor 5 (PDB: 6N51). MD simulations of sucrose-protein complexes and ligand-free receptors were carried out using GROMACS 2020 for at least 300 ns to underline the conformational effects induced by the ligand binding. Structural changes of the sweet receptor were evaluated by computing properties strictly linked to the receptor function, such as the hinge angle in the VFTMs, a measure of the closed/open state, and the distances between the TM domains (Figure 1). Dimensionality reduction techniques, such as principal component analysis (PCA), were also employed to pinpoint major structural rearrangements and global correlations linked to protein function.

Results

The presence of sucrose docked into the orthosteric binding site of the VFTM remarkably affects the conformational behaviour of the receptor. More in detail, the presence of the ligand alters the variation of the VFTM hinge angle (ϑ) and thereby the TM distance (d) (Figure 1). Data reduction techniques highlight the strict mechanical connection between the different domains composing the sweet receptor: the link constituted by the CRD allows the transmission of the conformational changes in the VFTM up to the TM domain, thus linking the compound recognition in the extracellular domain to the structural rearrangements of the TMs.

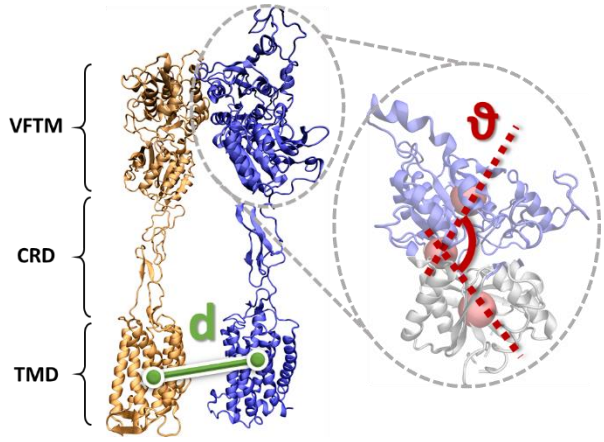

Figure 1: Molecular representation of the human sweet receptor with the reference to the computed VFTM hinge angle (ϑ) and TM distance (d).

Discussion

The detailed atomistic description of the MD simulation sheds light on the molecular mechanism that drives the activation of the human sweet taste receptor. The reported process is in line with the proposed activation mechanisms for other class C GPCRs [3]. These results increase the overall understanding of the complex and multiscale sweet taste perception process and pave the way for further studies aimed at design novel, food-based, enriched compounds to replace natural sugars with non-caloric sweeteners with a great impact on the human health status.

References

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