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Homology modeling and docking studies of human G-Protein coupled receptor involved in taste perception

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Abstract

A series of biochemical, electrophysiological and psychophysical studies suggest that proteinaceous receptors coupled to the G-protein/adenylate cyclase second messenger cascade mediate sweet taste for some compounds. To further predict the role of G proteins and to understand the mechanisms of interaction between sweetener, modulator and inhibitor binding, a three-dimensional model of the G protein coupled receptor (Accession Number: AAB94130) is generated based on the crystal structure of bovine rhodopsin (PDB: 1F88) by using the software MODELLER 7v7. The structure having a least modeller objective function was used as a starting point for picoseconds-duration molecular dynamics simulations. The final refined model contained seven transmembrane α-helices in common within this family of sequences. Superposition of the structure with the template showed Co-trace RMSD deviation of 0.7Å. The refined model was further assessed by ERRAT, WHATCHECK and PROCHECK, which indicated that the refined model is reliable with 83.9% of the residues in the core regions of the Ramachandran’s plot. Active site analysis showed that site1 is highly conserved with the catalytic site of the template, which is present on the extra cellular side of the membrane. Docking studies with sweeteners, modulators and newly designed molecules with the site1 of the refined model indicate that urea (4-cyanophenyl) is the preferred inhibitor with a binding score of -546.29. The docking studies revealed that Asp345, Asn319 and Ser155 of extra membrane region are important determinant residues as they have strong hydrogen bonding contacts with the ligand.

Keywords: GPCR, Homology modeling, Molecular dynamics, Docking.

INTRODUCTION

The largest class of cell surface receptors in mammalian genomes is the super family of G-protein-coupled receptors further referred as GPCRs. Of the approximately 1000 genes thought to encode GPCRs in humans, about 300 to 400 mediate the effects of endogenous ligands, with the remainder being sensory receptors. GPCRs mediate numerous physiological processes and also the sense of taste utilizing the adenylylate cyclase system as a second messenger and are the targets of many clinically important drugs (Drews et al., 1996). An amino terminal extracellular domain, a carboxyl-terminal intracellular domain and seven hydrophobic transmembrane domains characterize GPCRs structurally. The interaction of an agonist with a GPCR binding pocket elicits or stabilizes a conformational change in the receptor's transmembrane domains. This conformational change allows the receptor to associate with heterotrimeric G proteins and initiate a signaling cascade inside the cell leading to a physiological response (Lefkowitz et al., 1993). Historically, the activation and inhibition of GPCR function has been a very successful avenue for drug discovery and development. Marketed drugs for both GPCR agonists (e.g. Sumatriptan, 5-HT1 receptor) and antagonists (e.g. Loratidine; H2 receptor) exist and there are a number of compounds in clinical trials exploiting allosteric-