Molecular Insights into the Transmembrane Domain of the Thyrotropin Receptor

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Résumé en anglais

The thyrotropin receptor (TSHR) is a G protein-coupled receptor (GPCR) that is a member of the leucine-rich repeat subfamily (LGR). In the absence of crystal structure, the success of rational design of ligands targeting the receptor internal cavity depends on the quality of the TSHR models built. In this subfamily, transmembrane helices (TM) 2 and 5 are characterized by the absence of proline compared to most receptors, raising the question of the structural conformation of these helices. To gain insight into the structural properties of these helices, we carried out bioinformatics and experimental studies. Evolutionary analysis of the LGR family revealed a deletion in TM5 but provided no information on TM2. Wild type residues at positions 2.58, 2.59 or 2.60 in TM2 and/or at position 5.50 in TM5 were substituted to proline. Depending on the position of the proline substitution, different effects were observed on membrane expression, glycosylation, constitutive cAMP activity and responses to thyrotropin. Only proline substitution at position 2.59 maintained complex glycosylation and high membrane expression, supporting occurrence of a bulged TM2. The TSHR transmembrane domain was modeled by homology with the orexin 2 receptor, using a protocol that forced the deletion of one residue in the TM5 bulge of the template. The stability of the model was assessed by molecular dynamics simulations. TM5 straightened during the equilibration phase and was stable for the remainder of the simulations. Our data support a structural model of the TSHR transmembrane domain with a bulged TM2 and a straight TM5 that is specific of glycoprotein hormone receptors.

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