The dynamics of the conformational modulation of rhodopsin by the NPxxY motif in transmembrane helix 7 depends on the interaction of Y7.53 with F7.60 in the juxtamembrane helix 8

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Introduction

G-protein coupled receptors (GPCRs) are membrane proteins that can adopt multiple, functionally relevant conformational states in the course of selectively triggering specific cell signaling processes. Conserved structural microdomains in these proteins can act as molecular switches between these states. One such microdomain is the NPxxY motif in transmembrane (TM) helix 7 with the juxtamembrane helix 8 through an interaction observed in the crystal structure. Together, these structural elements comprise a motif identifiable as NPxxYx(5.6)F that seems to be conserved in the rhodopsin family of GPCRs and has been shown to modulate GPCR activation, phosphorylation and internalization.

To understand the role of this motif in the dynamic modulation of GPCR function we studied the behavior of the wild type rhodopsin and several mutants with molecular dynamics simulations in a fully hydrated lipid bilayer. The mutant constructs with changes at positions 7.53 and 7.60 (Y7.53F, Y7.53N/F7.60A, Y7.53F/F7.60A) were chosen to modify the nature of the interaction between these loci in order to evaluate a possible correlation with receptor dynamics.

Using molecular dynamics simulation, we are able to identify the immediate structural and energetic changes that occur via mutation of position 7.53 and 7.60 in rhodopsin. Collectively, these changes appear to alter the intracellular face of the receptor.

Structural Differences

Fig. 4. Most principal eigenvector describes a relative positional change between TM7 and HX8.

Left: Molecular model of the most positive projection (red) and the most negative projection (blue) of TM7-HX8, superimposed on TM7. Right: Projection values of the structures from the WT simulation onto the most principal eigenvector versus time.

Energetic differences

Fig. 6a. Interaction energies between TM7 and neighboring helices. TM7-TM2 and TM7-HX8

Interaction energies are presented as averages over time. (a) The following sets of residues were used for the calculations: TM7 (49-78), TM2 (4.2-50) and HX8 (7.60-7.70). (b) The entire residue (backbone and sidechains) was included for these calculations.

Conclusions

Using molecular dynamics simulation, we are able to identify the immediate structural and energetic changes that occur via mutation of position 7.53 and 7.60 in rhodopsin. Collectively, these changes appear to alter the intracellular face of the receptor.

Continuing analysis aims to identify how this network of interactions, consisting of the NPxxYx(5.6)F motif, N2.40 and L2.43, allosterically couples to portions of the receptor distal from this microdomain.

References


Molecular images were generated with VMD 1.8.4.