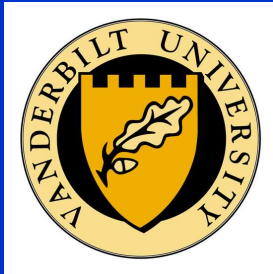


ESF-FWF Conference in Partnership with LFUI
Water Interfaces in Physics, Chemistry and Biology: A Multi-Disciplinary Approach
Universitaetszentrum Obergurgl (Oetz Valley, near Innsbruck), Austria
8-13 December 2007

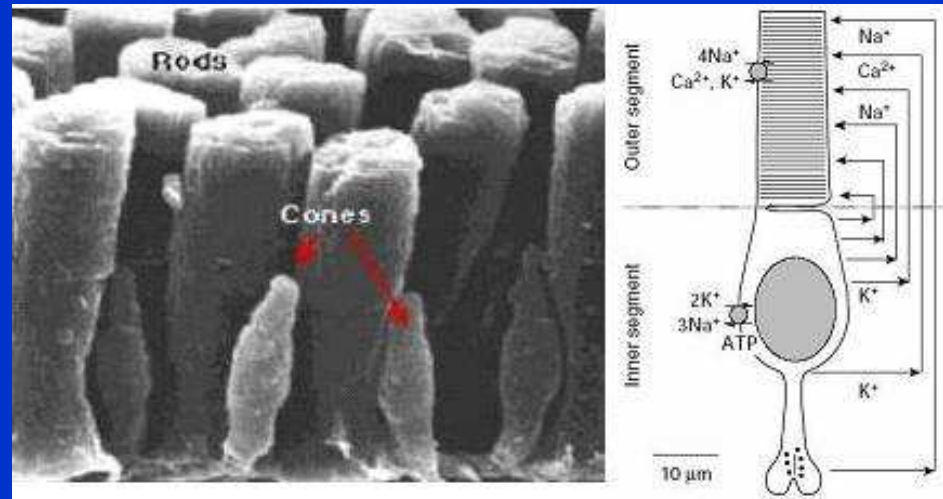
- **Hydration in GPCR-mediated signal transduction**
- Joseph Parello¹ , Lixin Shen¹, Jean-Louis Banères² & Michel Laguerre³
- ¹ Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, TN, USA
- ² Institut des Biomolécules Max Mousseron (IBMM), UMR 5247 CNRS, Montpellier, France
- ³ Institut Européen de Chimie et de Biologie (IECB), UMR 5248 CNRS CBMN, Pessac, France.
- **Abbreviation** : *G-protein coupled receptor (GPCR)*



Hydration in GPCR-mediated signal transduction

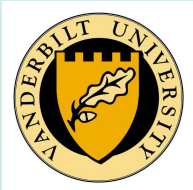
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Micrograph of salamander retina



Structural organization of a salamander rod

Rhodopsin
is a transmembrane G protein coupled receptor (GPCR)
involved in the vision process of a variety of organisms



Advances in Protein Chemistry

Volume 74, 2007, Pages 67-93

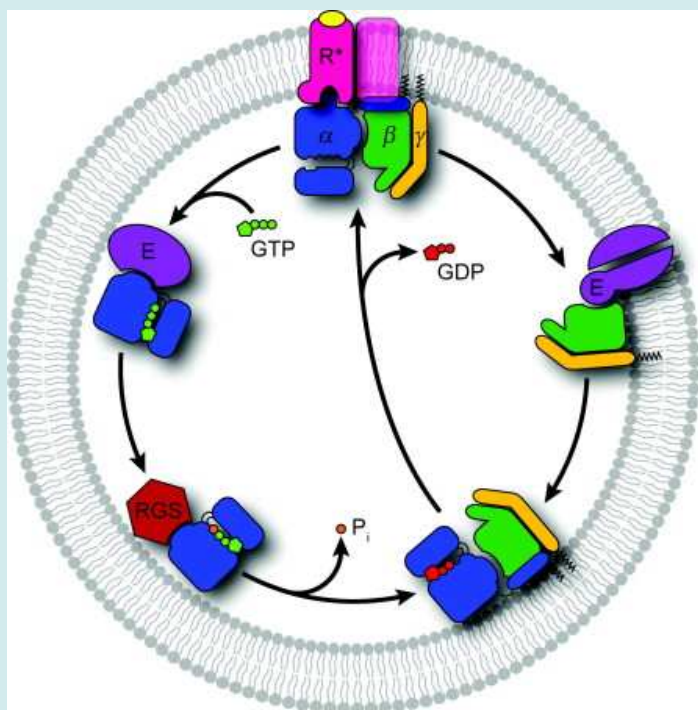
Mechanisms and Pathways of Heterotrimeric G Protein Signaling

How do Receptors Activate G Proteins?

William M. Oldham and Heidi E. Hamm

Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232

Available online 11 September 2007.



Heterotrimeric G proteins GDP-bound α (*blue*), β (*green*), and γ (*gold*) subunits.

Heptahelical receptor (*pink*) in the cell membrane

Downstream effector proteins (E, *purple*).

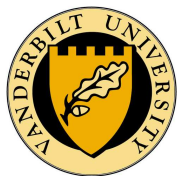
Signal terminated on the hydrolysis of GTP to GDP by $G\alpha$, which may be catalyzed by RGS proteins (*dark red*).

Fig. 1. Overview of the G protein cycle

The concept of an heptahelical organization for the transmembrane G protein coupled receptors rests upon the initial structural determination of the structure of bacteriorhodopsin (bRho)

Three-dimensional model of purple membrane obtained by electron microscopy
R.Henderson & P.N.T.Unwin, Nature 1975, 257, 28-32.

A 7-Å resolution map of the purple membrane has been obtained by electron microscopy of tilted, unstained specimens. The protein in the membrane contains **seven, closely packed, alpha-helical segments which extend roughly perpendicular to the plane of the membrane for most of its width.**



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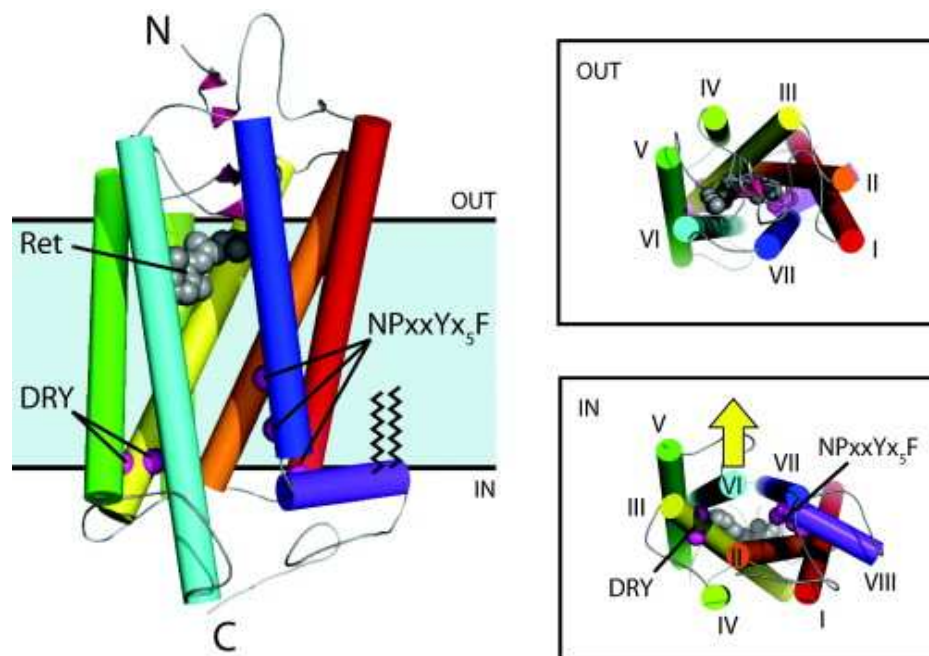
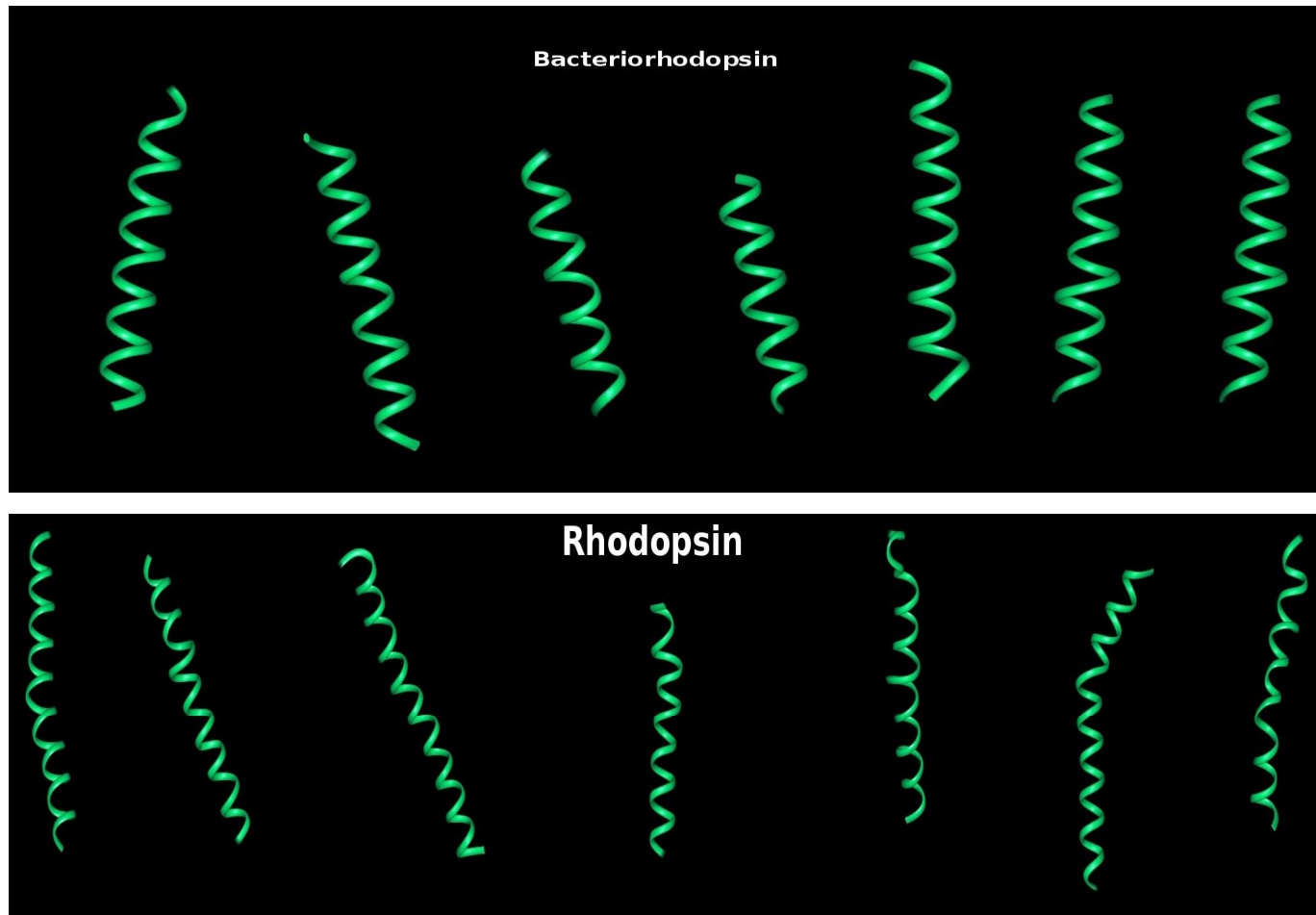


Fig. 2. Structure of a heptahelical receptor.

Cartoon model of dark (inactive) bovine rhodopsin (1U19), showing the seven transmembrane-spanning α helices (red to blue) and 11-*cis*-retinal (gray spheres).

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- Crystal structure of the unique parvalbumin component from muscle of the leopard shark (*Triakis semifasciata*). The first X-ray study of an alpha-parvalbumin.
- Roquet F; Declercq J P; Tinant B; Rambaud J; Parello J *J Mol Biol* 1992, **223**, 705-20.

Introduction of the plots

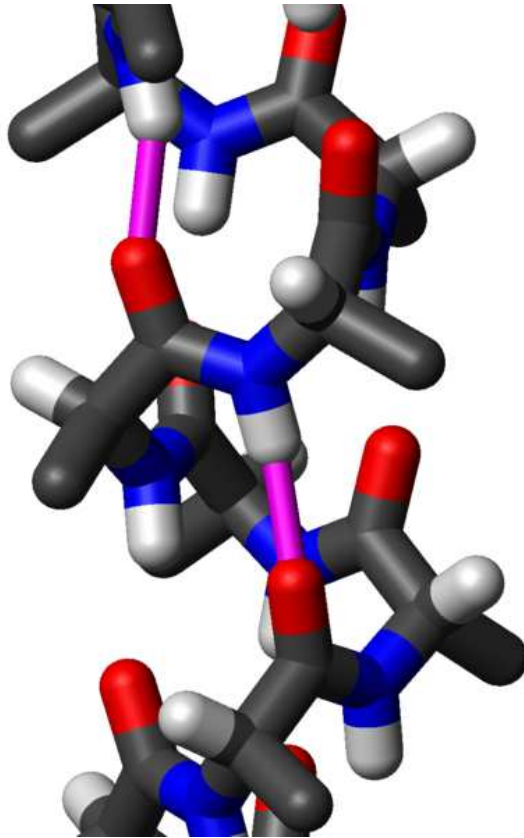
distance (O_i/N_{i+3} , O_i/N_{i+4}) versus residue i

to visualize the local geometry of alpha-helices in the protein 3D-structures

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Alpha helix



Close-up sideview of a "stick" model of an alpha helix of poly-alanine using the dihedral angles $\varphi=-60^\circ$ and $\psi=-45^\circ$ and the Engh&Huber bond geometry. Two hydrogen bonds are highlighted in magenta; the O-H distance is 2.08 Å.

From Wikipedia, the free encyclopedia

The $O_i \dots Ni+3$ and $O_i \dots Ni+4$ distances are "magic" distances since they bring together a C=O group (i residue) and two NH groups ($i+3$ and $i+4$ residues) at hydrogen bond distance.

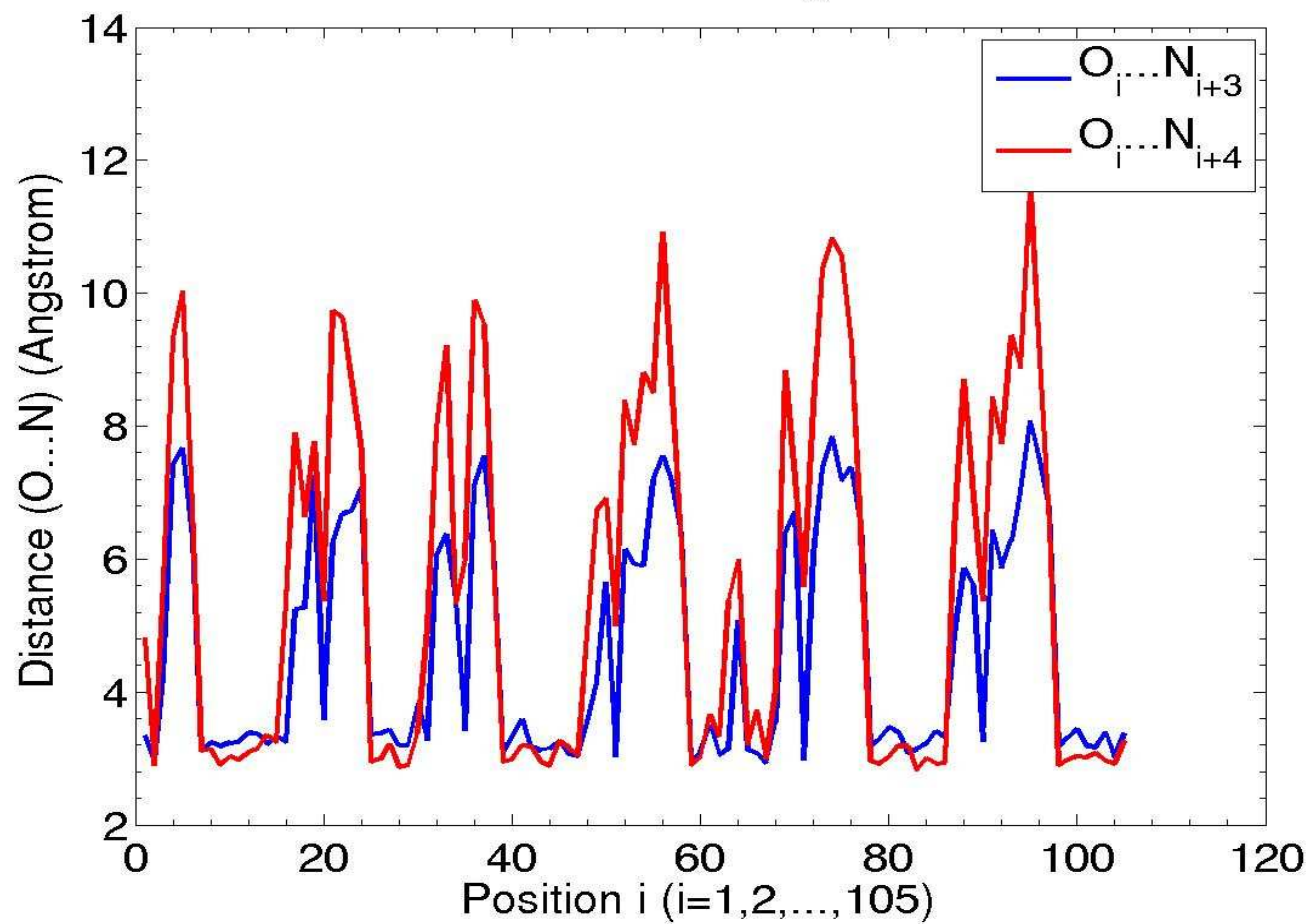
In the regular alpha-helix we have :

$$\text{distance}(O_i \dots Ni+3) > \text{distance}(O_i \dots Ni+4)$$

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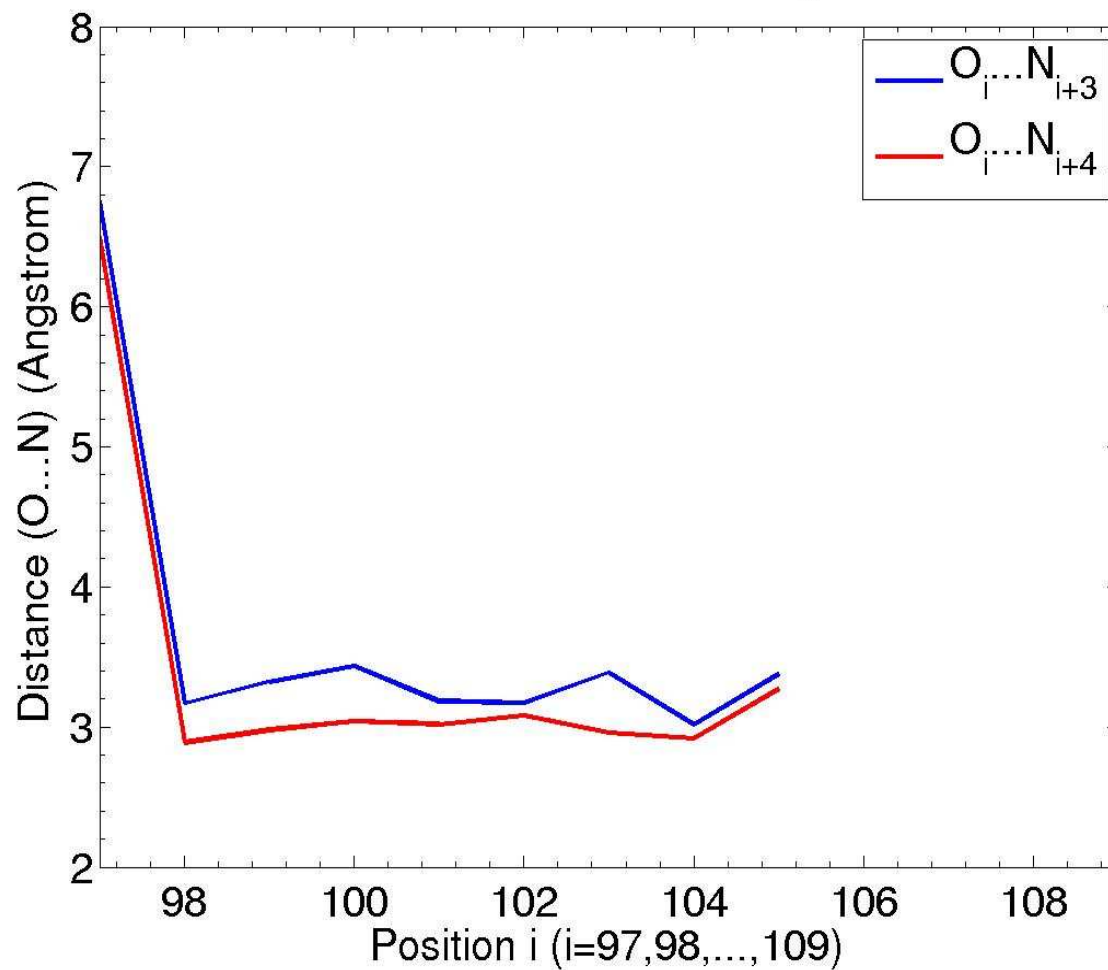
Parvalbumin 5PAL at 1.54 Angstroms Resolution



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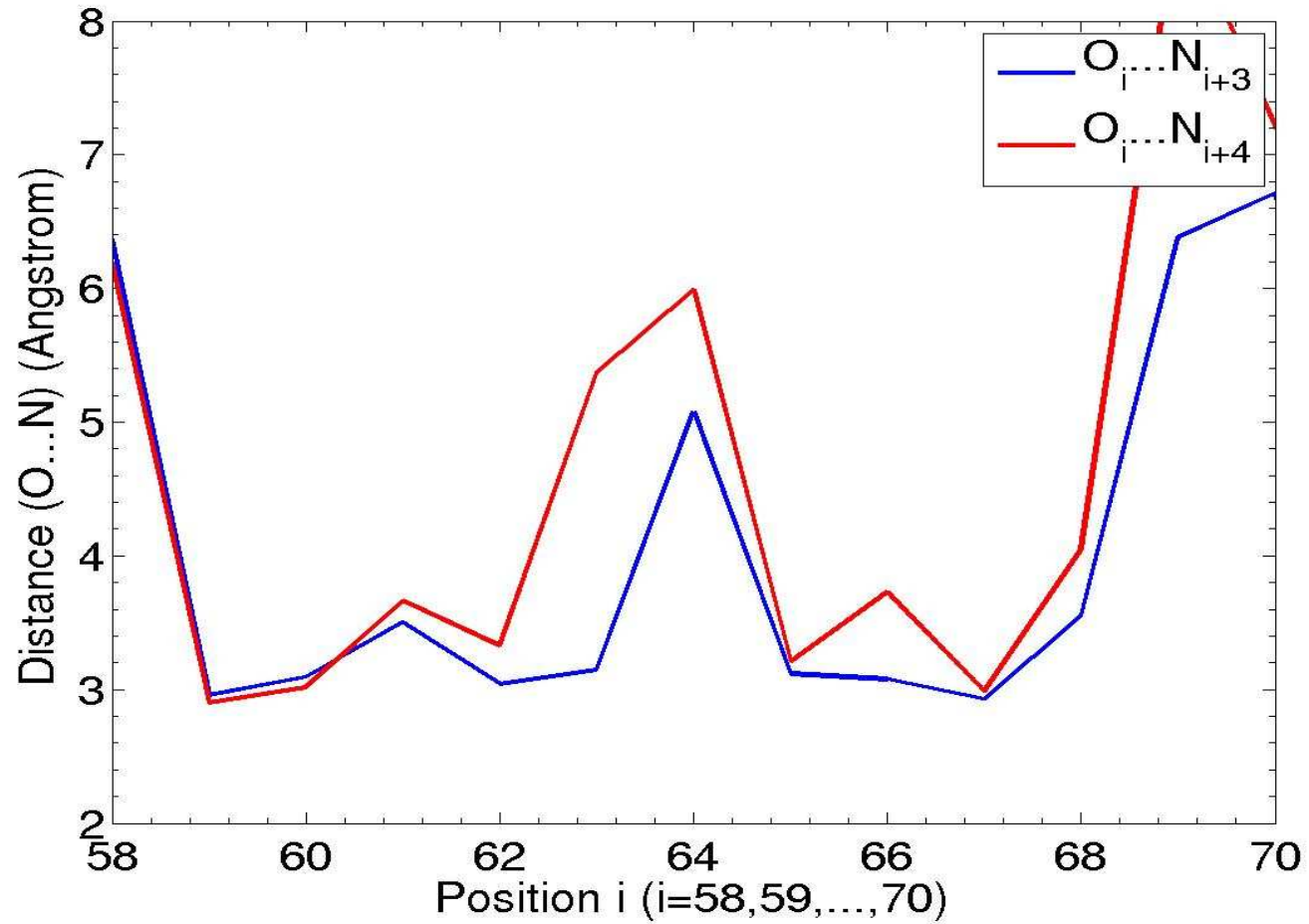
Helix 6 of Parvalbumin 5PAL at 1.54 Angstroms Resolution



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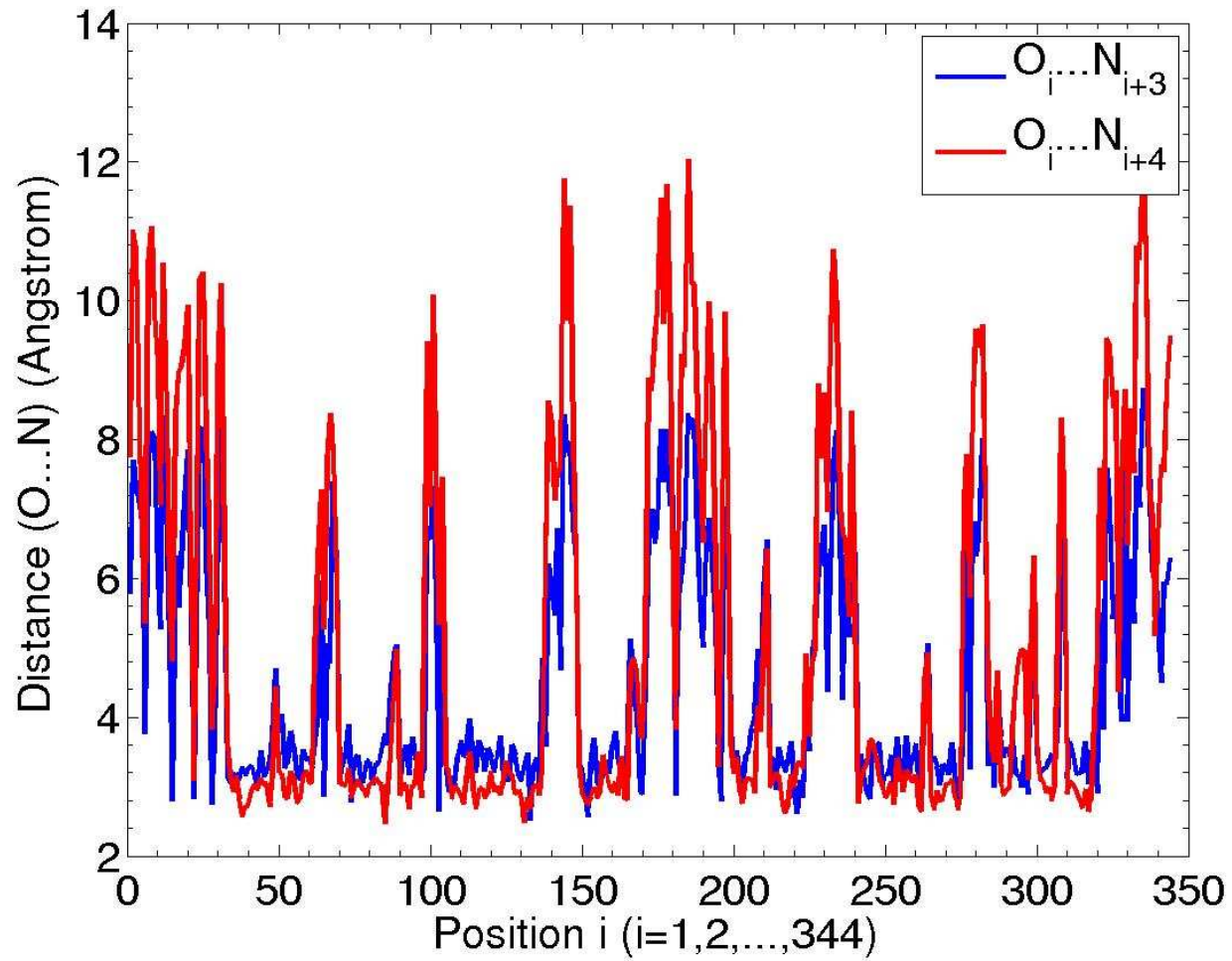
Helix 4 of Parvalbumin 5PAL at 1.54 Angstroms Resolution



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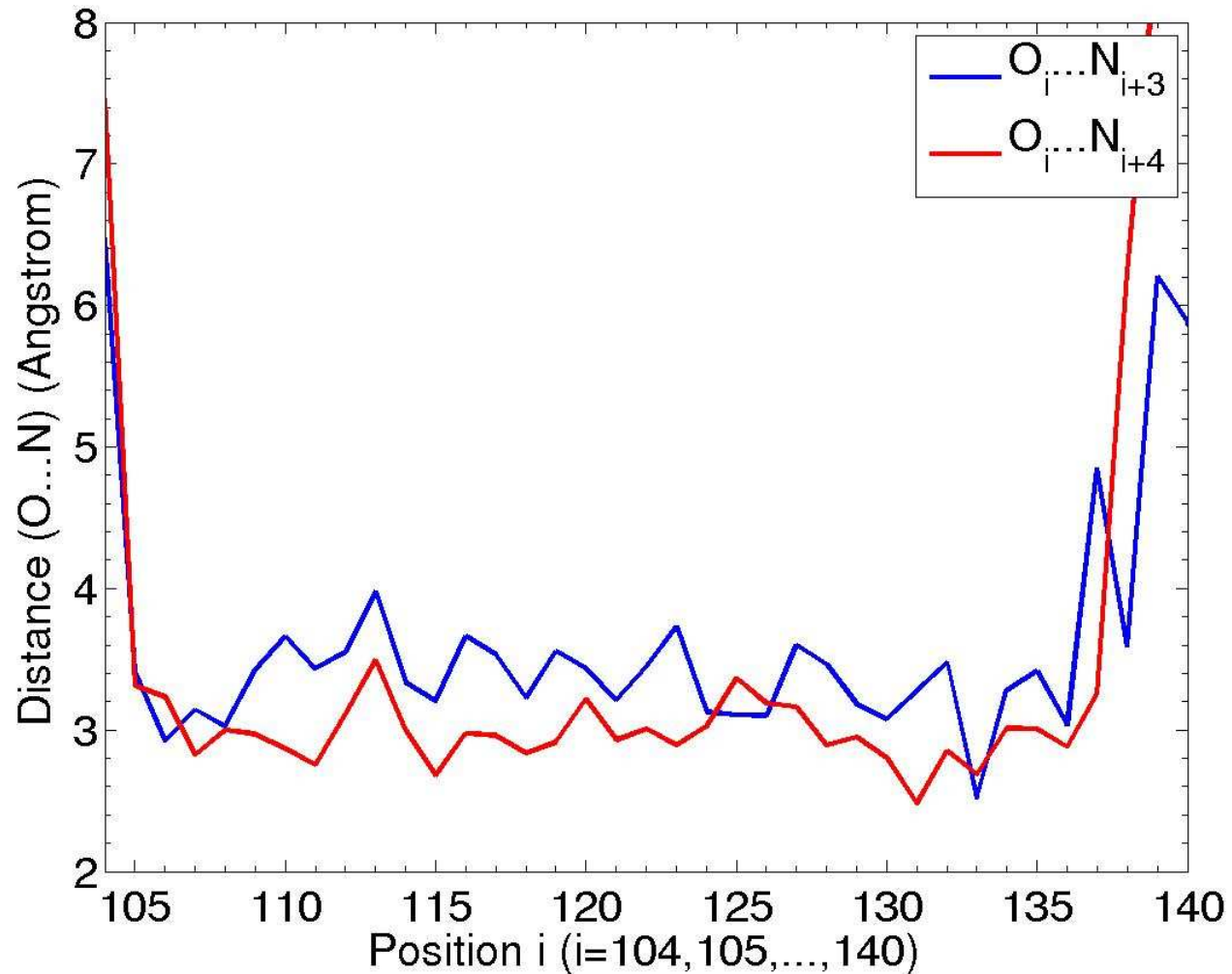
Rhodopsin 1U19 at 2.20 Angstroms Resolution



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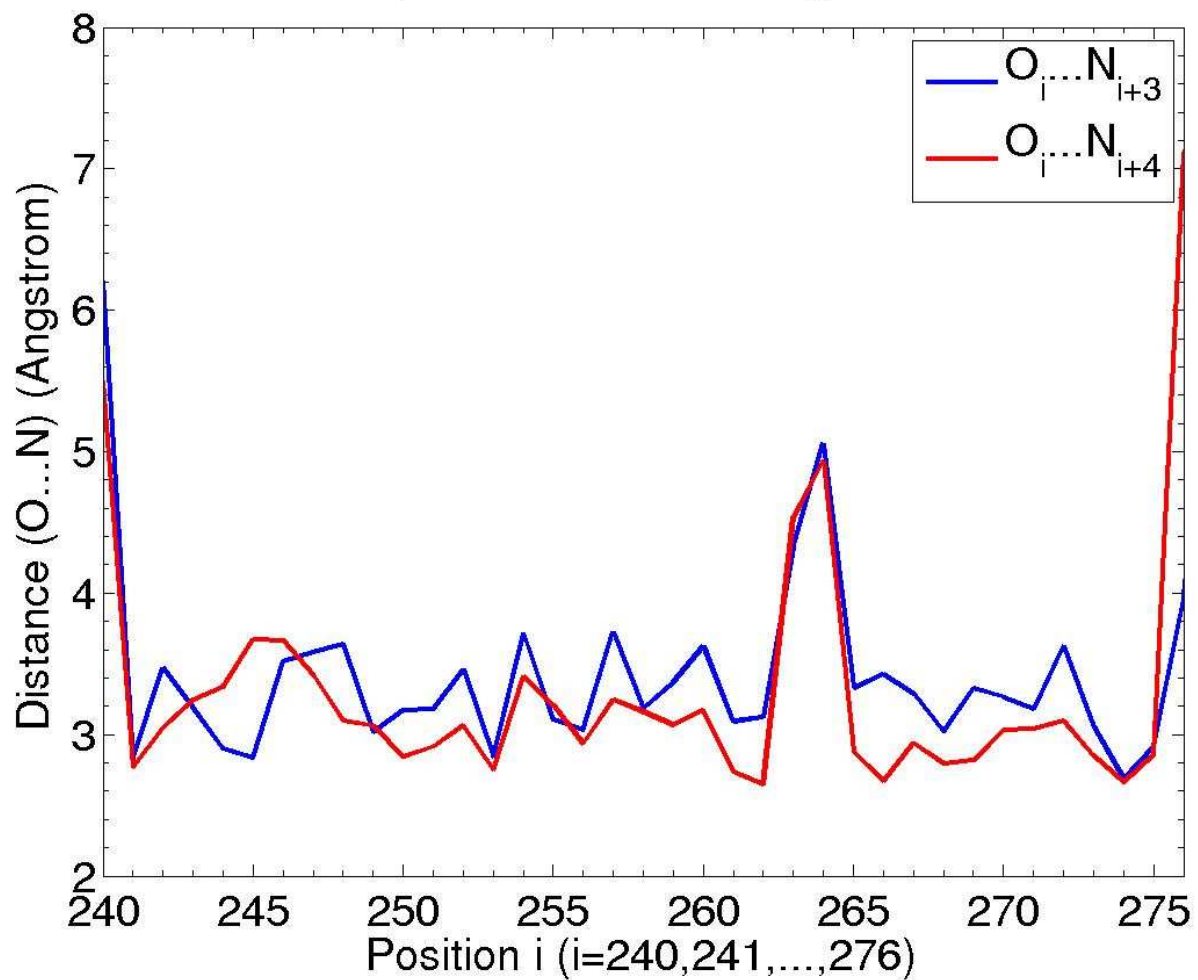
TM 3 of Rhodopsin 1U19 at 2.20 Angstroms Resolution



Hydration in GPCR-mediated signal transduction

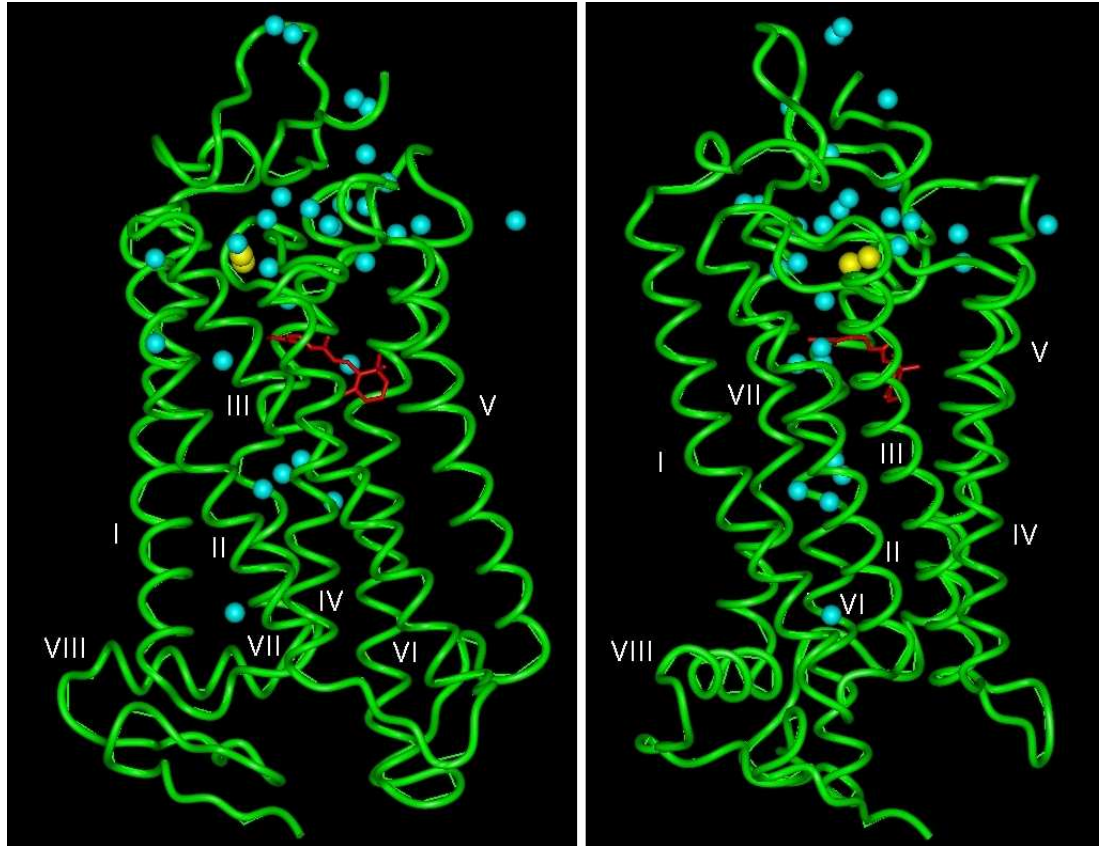
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TM 6 of Rhodopsin 1U19 at 2.20 Angstroms Resolution



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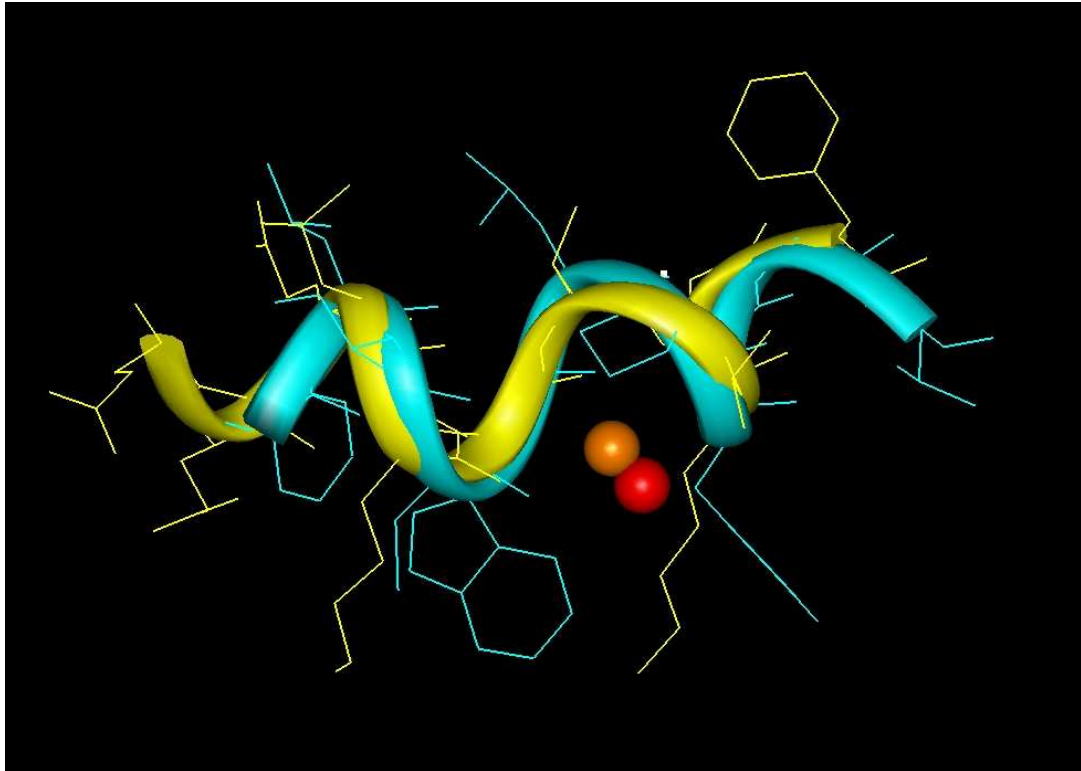
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Hydration of bovine rhodopsin in the crystal structure 1U19

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Selective hydration of two kinked alpha-helices with highly related geometries

Blue: helix TM6 of bovine rhodopsin 1U19

Yellow: helix 4 (or helix D) of parvalbumin 5PAL

Structure-based Analysis of GPCR Function: Conformational Adaptation of both Agonist and Receptor upon Leukotriene B4 Binding to Recombinant BLT1

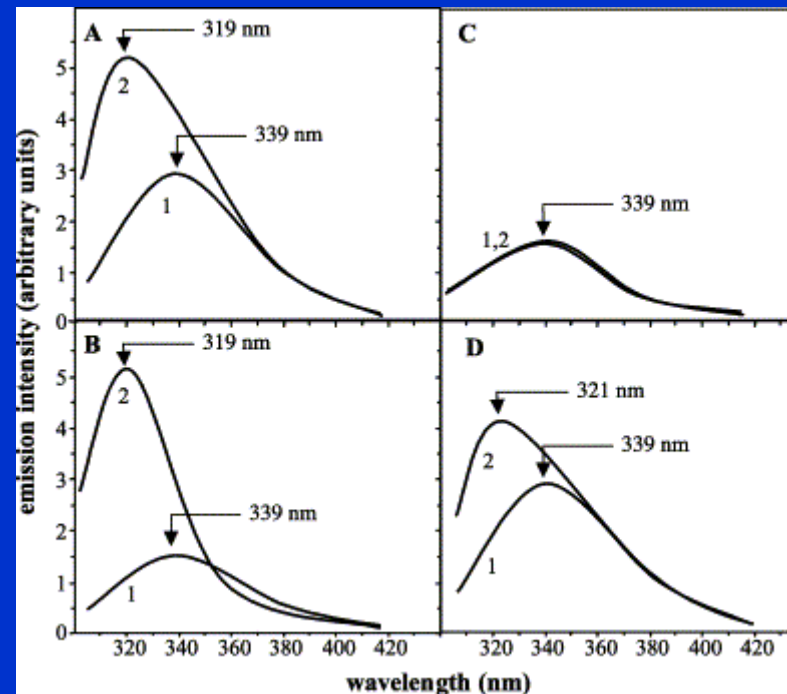
Jean-Louis Baneres, , Aimée Martin, Pierre Hullot, Jean-Pierre Girard, Jean-Claude Rossi and Joseph Parello, *J Mol Biol* 2003,329, 801-814

Activation of a rhodopsin-like GPCR by its natural agonist

(profiles 1: free receptor; profiles 2: agonist-loaded receptor)

All Trp included
wt receptor

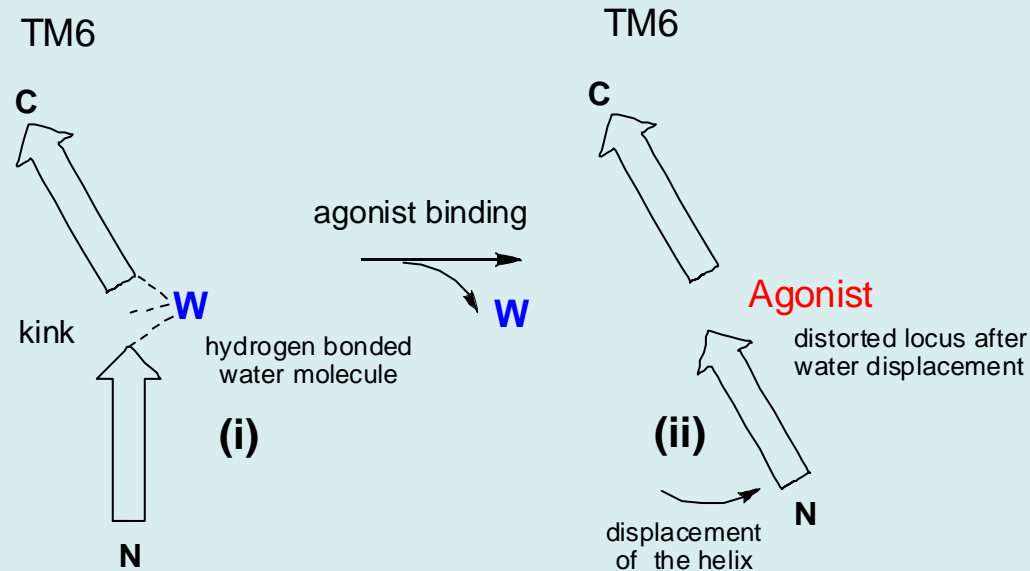
All Trp mutated for
Leu except Trp in TM6
(kinked region)



All Trp conserved
except Trp in TM6
mutated for Leu
(kinked region)

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Hypothetical model showing the role of the central water (W) molecule at the level of the kinked region of TM6 in a GPCR: schematic presentation of the helix in the absence of agonist in the presence of water (i) and after agonist binding upon water displacement (ii)

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● Acknowledgements

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- Dr Heidi Hamm, Chair Department of Pharmacology, Vanderbilt University School of Medicine, for her continuous interest
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