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Structure and Activation of the Visual Pigment Rhodopsin

by Steven O. Smith, 2010

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Rhodopsin is a **G** protein-coupled receptor (GPCR)

In which G protein stands for
guanine nucleotide-binding **protein**.

G-protein binds guanosine triphosphate (**GTP**) and
guanosine Diphosphate (**GDP**).

Therefore they can act as a switch:

G protein+GTP= On/activ

G protein+GDP= Off/inactiv

GPCR: Overview

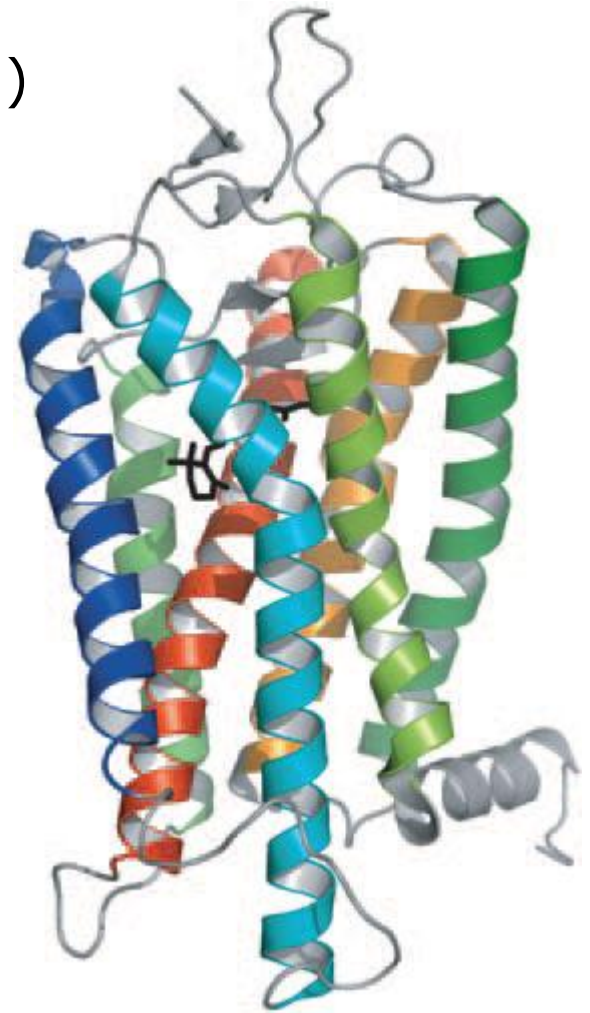
GPCRs have a 7 transmembrane helix (**7TM**) structure.

They can be activated in different ways
e.g. by ligands or photons

They play an important role in a wide variety of physiological processes. Like:

- Sensory
- Neurotransmission
- Hormones

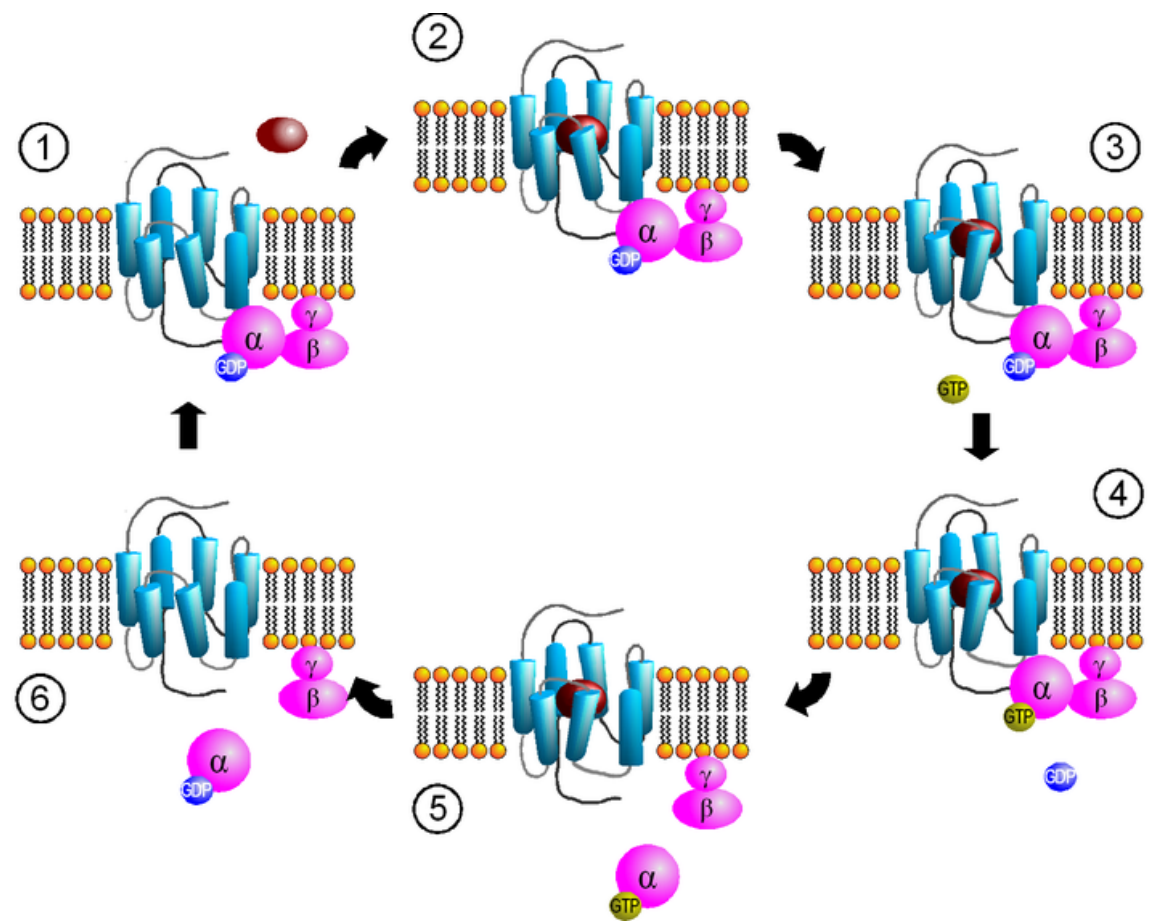
-> GPCRs are target of about 50% of drugs currently on market.



Crystal structure of Rhodopsin
Steven O. Smith Annu. Rev. Biophys. 39:309-28(2010)

GPCR: Overview

(active) GPCR catalyze the exchange of GTP for GDP in G protein.



Source: Sven Jähnichen, Wikipedia

Recent phylogenetic studies (*Fredriksson et al., Mol. Pharmacol. 2003*) lead to the **GRAFS** classification system of GPCRs.

According to **GRAFS** system the five main families of GPCRs are:

Glutamate

Rhodopsin

Adhesion

Frizzled/Taste 2

Secretin

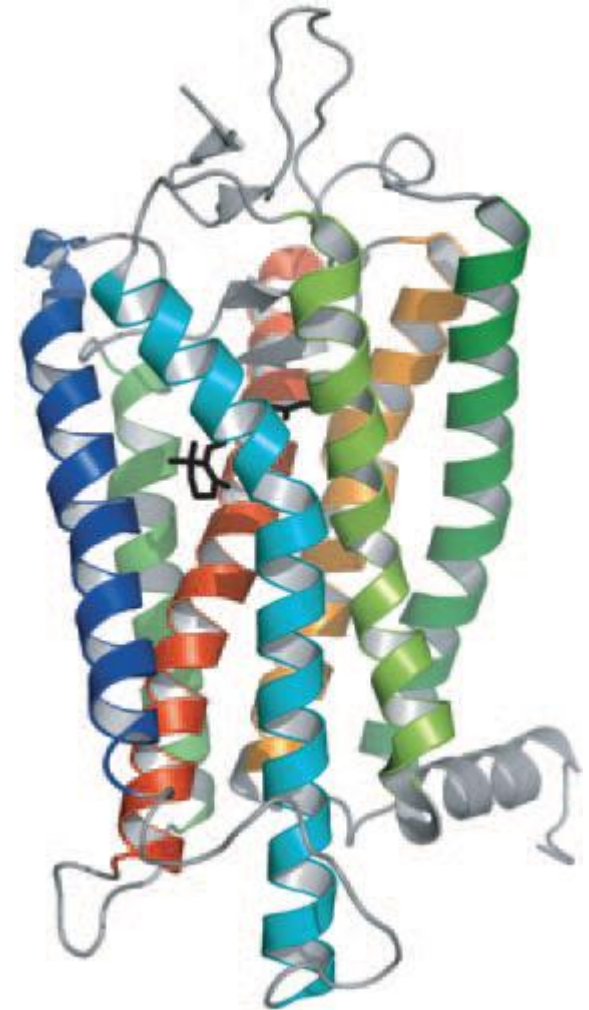
The rhodopsin family is additional divided in 4 subfamilies α , β , γ and δ .

Rhodopsin: Overview

~670 of the approximately 800 GPCRs are member of the rhodopsin family.

Rhodopsin is the best and most researched GPCR.

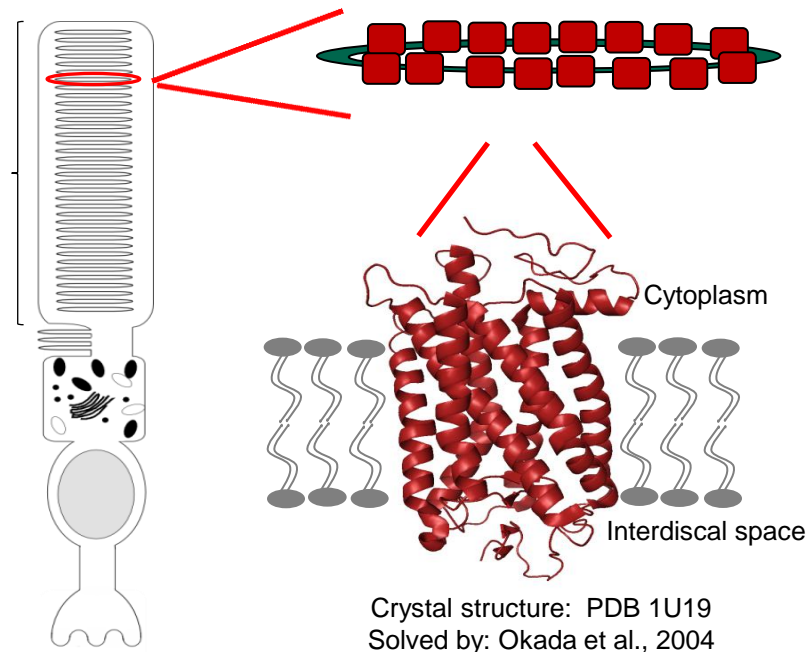
It was the first GPCR, which crystalline structure was solved.
(Palczewski *et al.*, *Science* 2000)



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Rhodopsin: Task

Human **R**od **o**uter **s**egments (ROS) are $\sim 40 \mu\text{m}$ in lengths and contain 1000-1500 discs, which each contain $\sim 100,000$ rhodopsin molecules



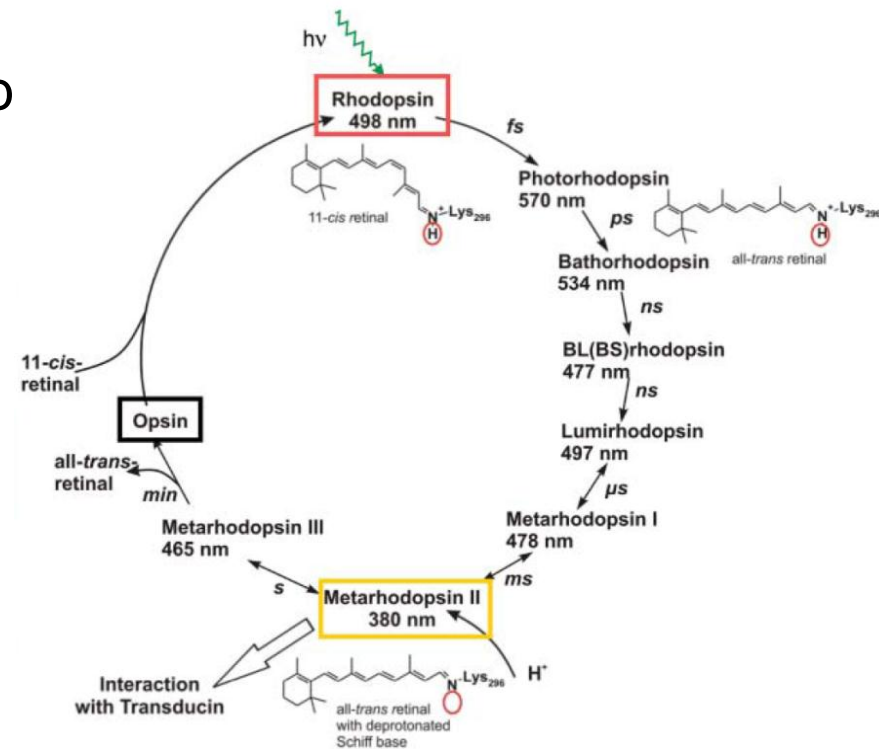
Source: Christina Seidler, AG Alexiev

Rhodopsin: Task

A single photon can induced the isomerization of the 11-*cis* retinal to the all-*trans* conformation.

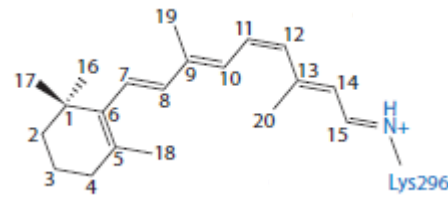
Activation of rhodopsin ->
Binding of G protein transducin

Activated transducin ->
Signaling Cascade ->
Picture



Kirchberg et al., Photochem. Photobiol. Sci. 9, 226-233 (2010)

Rhodopsin: Structure

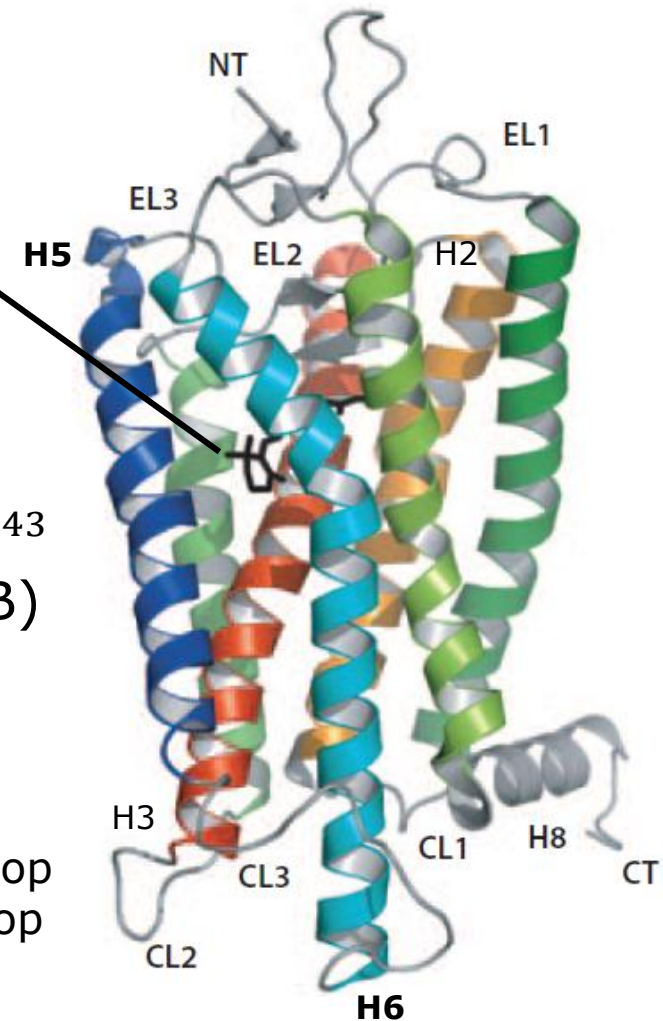


11-*cis* retinal

Opsin + retinal = Rhodopsin

The 11-*cis* retinal is attached to Lys296^{7.43} through a **protonated Schiff's base (PSB)** linkage.

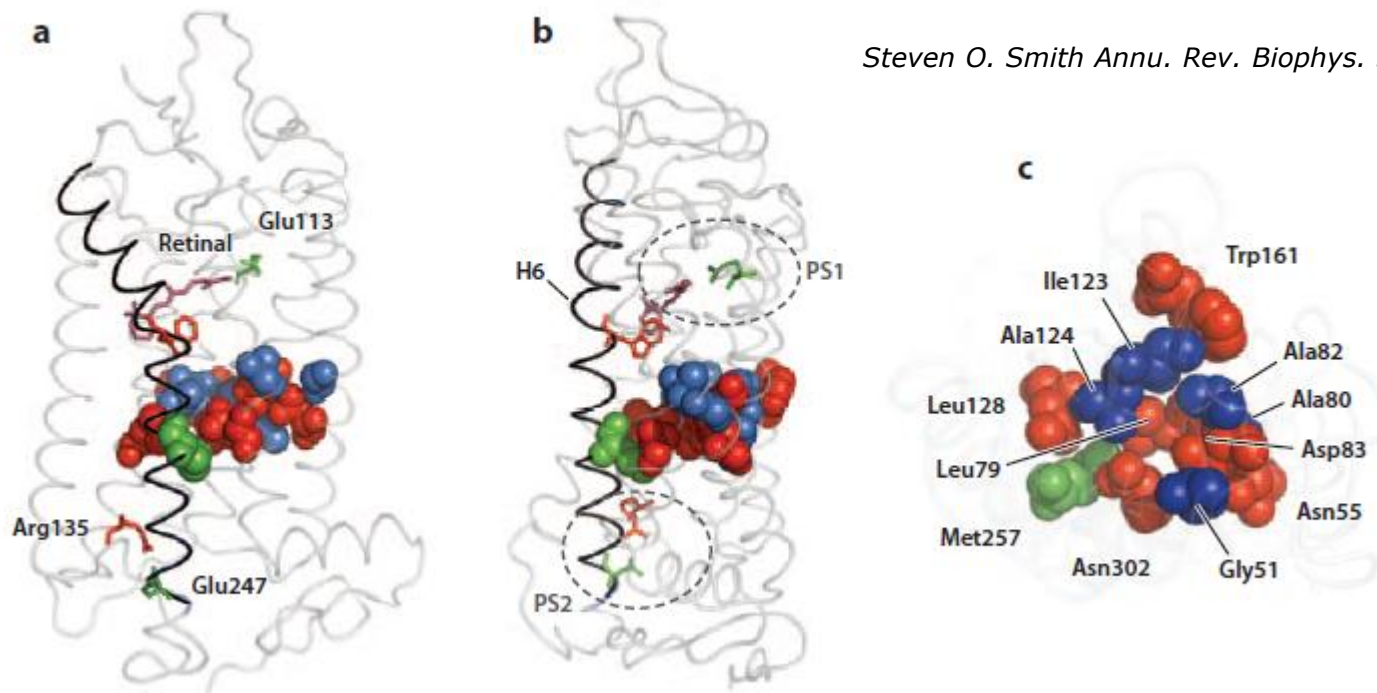
NT = N terminus
CT = C terminus
EL = extracellular loop
CL = cytoplasmic loop
H = Helix



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Rhodopsin: Protonation switches



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Glu113^{3.28} – PSB = **P**rotonation **S**witch 1(PS1)

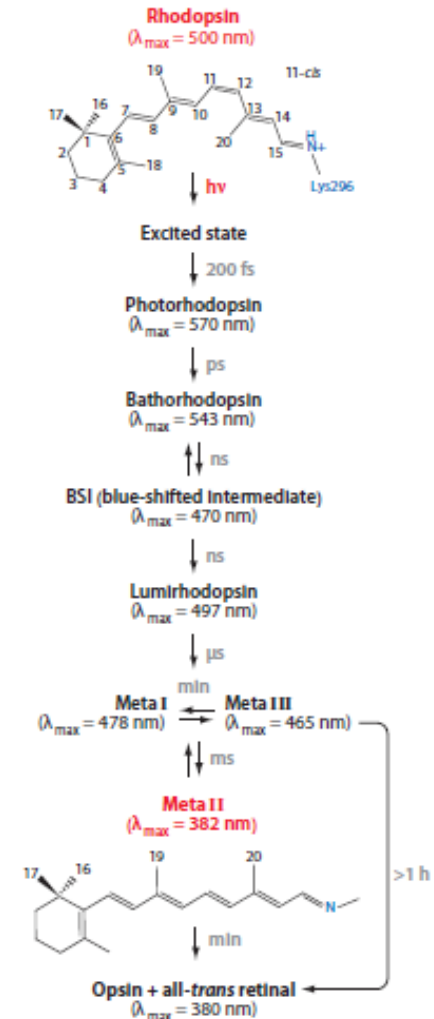
Arg135^{3.50} – Glu247^{6.30} salt bridge = PS2

Rhodopsin: Light activation

The quantum yield for isomerization of the 11-*cis* retinal PSB in solution ~ 0.3 and generates a mixture of different retinal isomers. Statistically only a single receptor is thermally activated every **470 years**.

The quantum yield for isomerization to all-*trans* retinal in the Rhodopsin binding pocket is ~ 0.67 ! The photoisomerization occurs in **200 fs**!

This is due a pretwist in the C11=C12 bond and the position of the Glu181 side chain, which facilitate isomerization by lowering the C11=C12 bond order

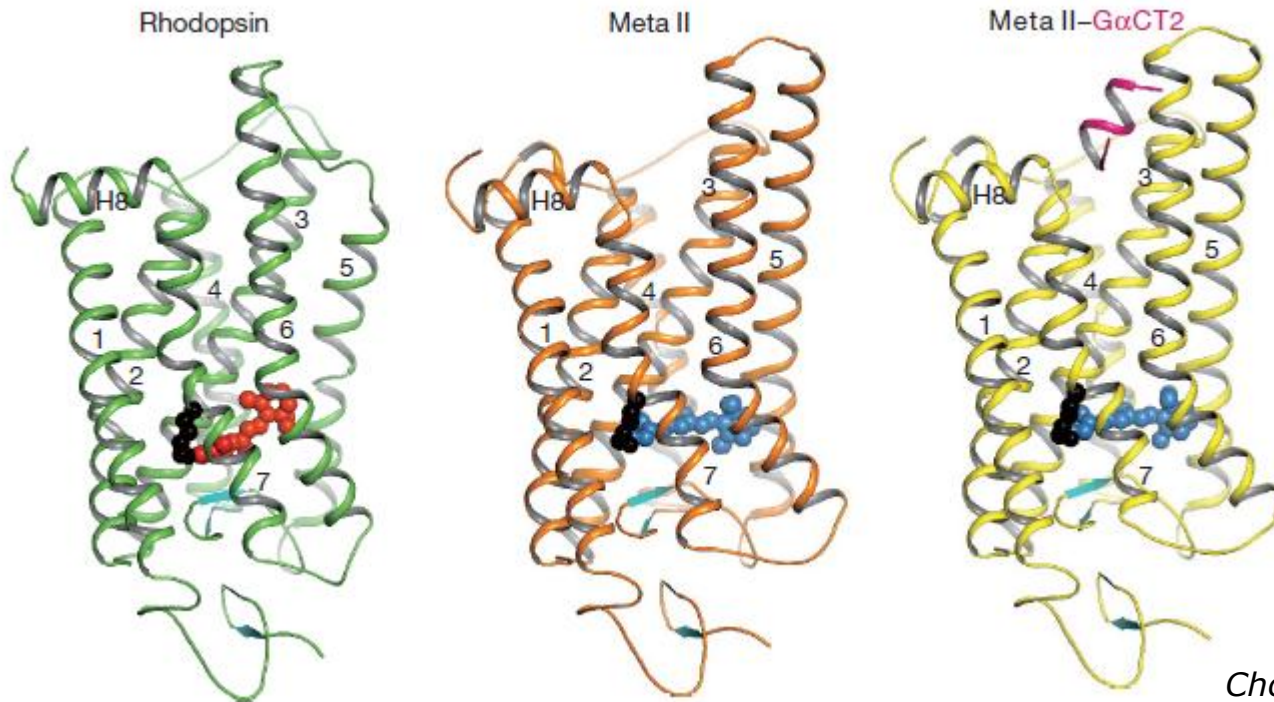


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Rhodopsin: Light activation

Retinal isomerization opens locks and leads to strong steric interactions

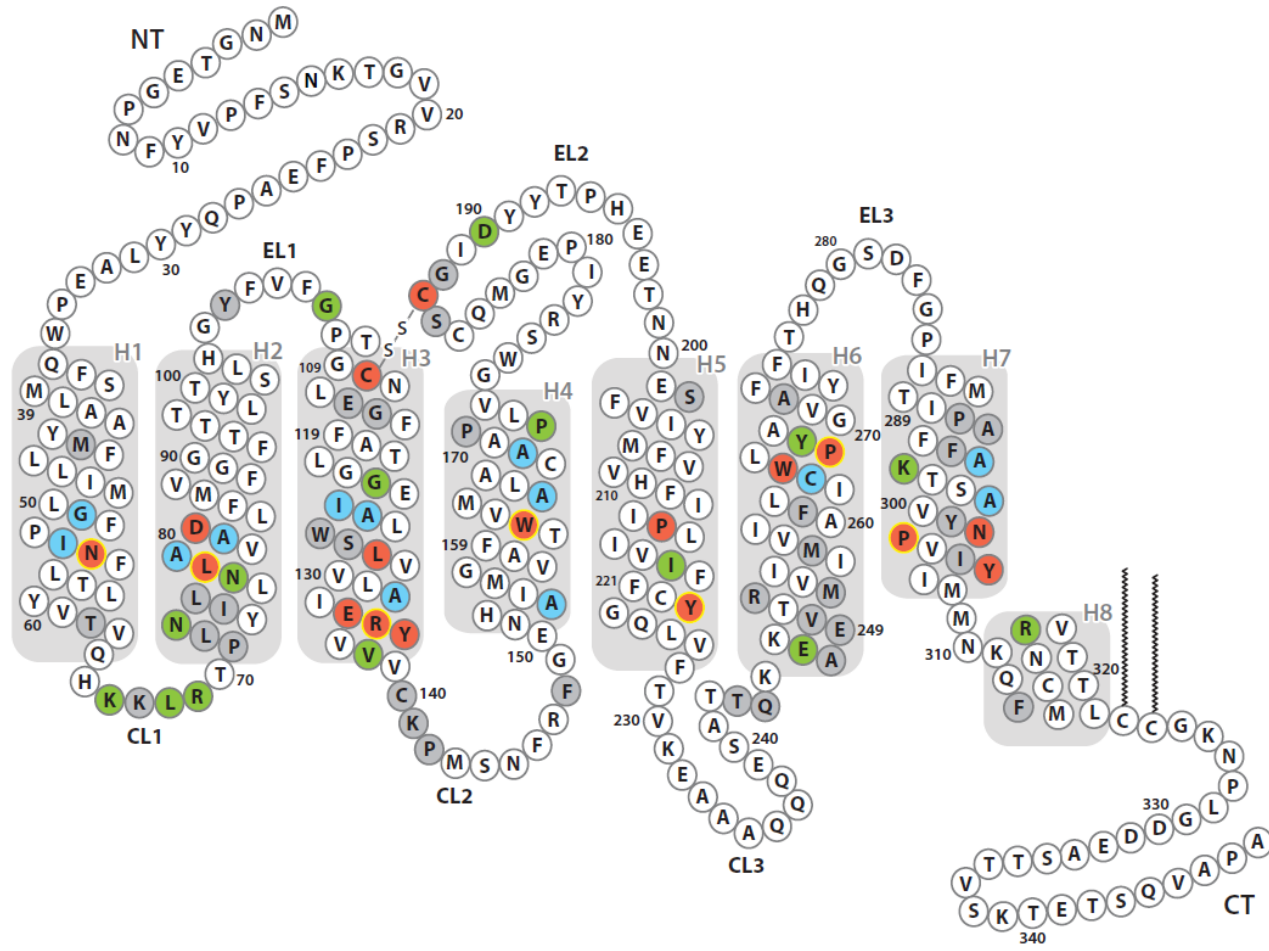
- > H5 is pushed up
- H6 rotates



Choe et al., Nature 2011

Rhodopsin as Model: Overview

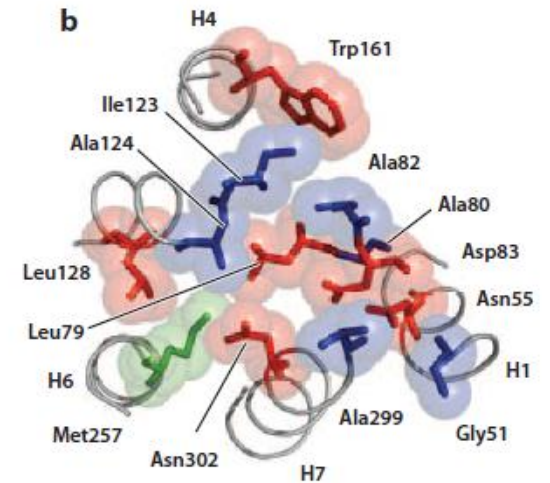
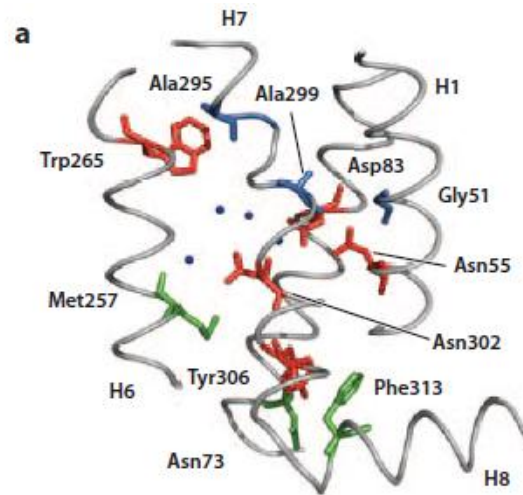
- Small and weakly polar group-conserved
- Subfamilies-specific residues
- 70% - 90% conserved residues
- Signature-conserved residues
- Highest sequence identity of each helix



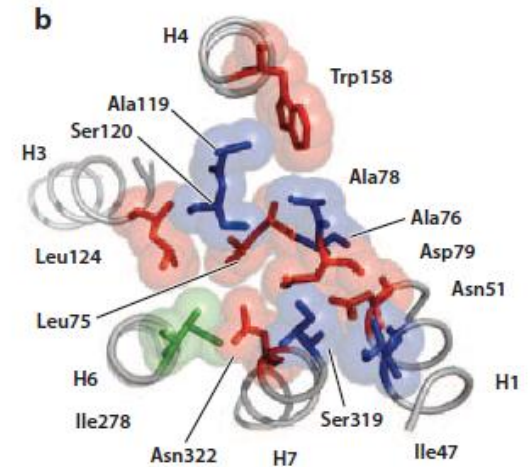
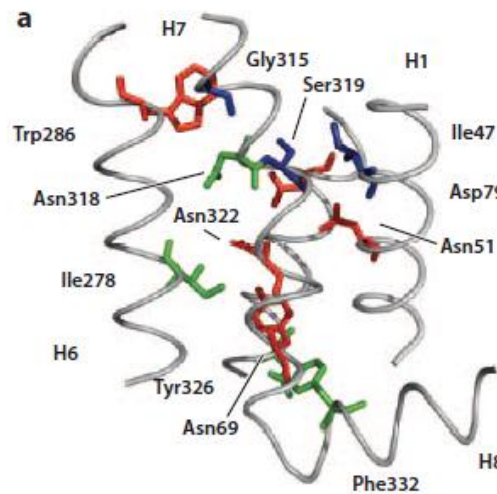
Steven O. Smith *Annu. Rev. Biophys.* 39:309-28(2010)

Rhodopsin as Model: Conserved Residues in Comparison

Rhodopsin

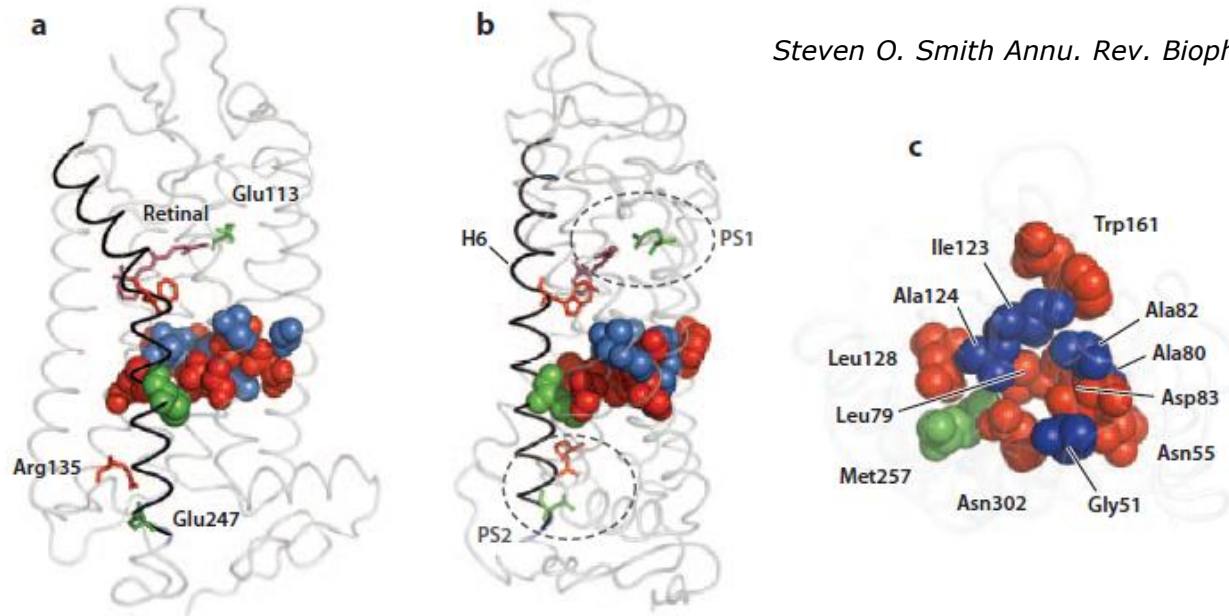


β_2 -Adrenoreceptor



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Rhodopsin as Model: Ligand-activated opsin



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Mutation of Met257^{6.40} allows activation of opsin by the addition of all-*trans* retinal as diffusible ligand.

For example, the M257I mutation exhibits 4.4% opsin activity, 1% activity with bound 11-*cis* retinal and 71% activity with the addition of all-*trans* retinal

Outlook: Future Issues

- Role of water in receptor activation.
- The role of receptor dynamics an the membrane environment.
- How do the signal of receptor binding with G protein reach the GDP binding site of the G protein to facilitate GDP->GTP exchange?
- How is activated rhodopsin recognized by and interacts with rhodopsin kinase?

Explanation: Subfamilies of the rhodopsin family

α -subfamily: amine binding receptors, several peptide binding and prostaglandin receptors.

β -subfamily: includes only peptide binding receptors

γ -subfamily: many peptide binding receptors such as chemokine receptors, some receptors that's bind neuropeptides

δ -subfamily: olfactory receptors, purin and glycoprotein receptors.

Explanation: Ballesteros-Weinstein Generic Numbering

[Amino acid]^[helix]. [position relative to most conserved amino acid (designated 50)]

e.g.

Trp265^{6.48} = Tryptophan 265 on helix 6. 2 residue towards N-Terminus of the most conserved amino acid.

Met6^{NT.53} = Tryptophan 6 on the N Terminus. 3 residue towards C-Terminus of the most conserved amino acid.

Trp250^{5.50} = Tryptophan 250 on helix 5. It is the most conserved amino acid.