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Molecules in focus

# Rhodopsin: Structure, signal transduction and oligomerisation

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ABSTRACT

Rhodopsin was the first G protein-coupled receptor (GPCR) for which a high-resolution crystal structure was obtained. Several crystal structures have now been solved representing different activation states of the receptor. These structures, together with those from lower resolution techniques (e.g. electron microscopy), shed light on the stepwise process by which energy from an extracellular photon is transduced across the membrane to the intracellular compartment thereby activating signalling mechanisms responsible for very low-level light detection. Controversy remains in several areas including: (i) transmembrane helix movements responsible for the transduction process, (ii) the stoichiometry of coupling to G proteins and their mode of activation, (iii) the role, if any, of receptor oligomerisation and (iv) the suitability of using structures of this GPCR as templates for modelling the structures of other GPCRs, and their mechanisms of activation.



## 1. Introduction

G protein-coupled receptors (GPCRs) currently hold a special place in the field of eukaryotic cell biology. They comprise one of the largest known families of integral-membrane proteins (1000–2000 members in vertebrates; >1% of the genome) and are the target of more than 30% of therapeutically relevant drugs for humans (Wise et al., 2002).

The prototypic GPCR rhodopsin (rod opsin; rod pigment; retinal dim-light photoreceptor; visual purple) is the pigment found in specialised neurons of the retina, rod photoreceptor cells, primarily responsible for dim-light vision in vertebrates (Okawa and Sampath, 2007). It is a member of the Class A (or Family 1) GPCRs, which represents ~90% of known GPCRs and is comprised largely of odorant and chemokine receptors (Bockaert and Pin, 1999). As with all GPCRs, rhodopsin is a 7-transmembrane protein (Fig. 1) which transduces a signal received from the extracellular space to the interior of the cell. In this case, the signal or 'ligand' consists of a photon interacting with a covalently bound retinal resulting in chemical and conformational changes in the structure of both retinal and the protein moiety (opsin). The activated receptor then stimulates a signalling cascade beginning with binding and activation of hundreds of molecules of the trimeric G protein, transducin, and resulting in rod photoreceptor cell hyperpolarisation, and synaptic signalling to adjacent rod bipolar cells. This exquisitely sensitive process allows dim-light monochromatic (scotopic) vision with detection of as few as 5 photons (Okawa and Sampath, 2007).

Rhodopsin has proved amenable to intense study in part because of its stability and abundance (it is packed into the membrane discs located within the outer segment of the rod photoreceptor cells). Ultimately, this has led to low-resolution electron microscope (EM) structures of the protein (Unger et al., 1997) and the first high-resolution crystal structures of a GPCR (Palczewski et al., 2000). These studies and the considerable amount of information derived from a range of biochemical and biophysical methods have illuminated many details of rhodopsin structure and activation in particular, and GPCR structure and activation in general. Not surprisingly, however, this correlative approach is not always successful (e.g., Archer et al., 2003) and is probably a reflection of the wide diversity of GPCR sequences, ligands (e.g. photons, small organic molecules, proteins), ligand-binding locations, and allosteric effectors.

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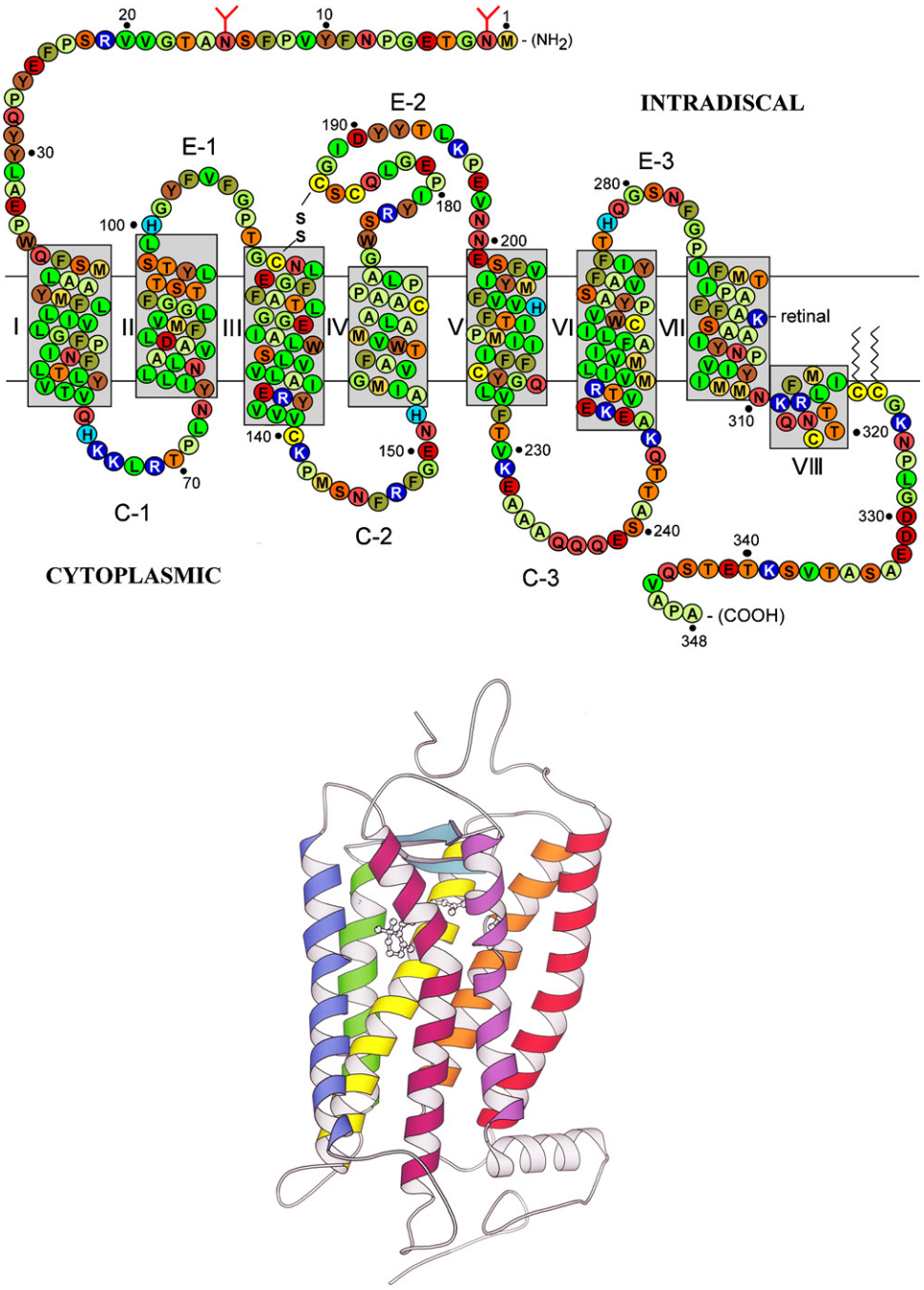


**Fig. 1.** Upper panel: sequence of human rhodopsin in single-letter code showing the locations of the seven transmembrane helices (HI-VII), HVIII lying adjacent and parallel to the membrane, the intradiscal (E1-3) and cytoplasmic (C1-3) loops, and the N- and C-terminal domains. N2 and N15 are sites of glycosylation. The highly conserved disulphide bridge between C110 and C187 lies above retinal, which forms a protonated Schiff base with the ε-amine group of K296 in HVII. Palmitoyl moieties anchor C322 and C323 to the membrane. Lower panel: 3D structure of the inactive (dark) state of bovine rhodopsin as seen through the plane of the membrane with the intradiscal side at the top and the cytoplasmic side at the bottom. The transmembrane helices proceed in an anti-clockwise direction as viewed from the intradiscal side. HI (red), HII (orange), HIII (yellow), HIV (green), HV (blue), HVI (crimson), HVII (purple). The cytoplasmic helix, HVIII, is shown in grey. 11-*cis* Retinal is shown as a ball and stick model. The structure was generated using Molscript. The bovine and human proteins are 93% identical.

## 2. Structure

As with all GPCRs, rhodopsin consists of: (i) an 'extracellular' N-terminal domain (in this case, the 'extracellular' side is actually the intradiscal side of the disc membrane), (ii) a bundle of 7 mostly α-helical transmembrane domains (HI-VII) proceeding anti-clockwise as viewed from the intradiscal side and linked in series by 3 extracellular loops (E1-3) and 3 cytoplasmic loops (C1-3), and (iii) a cytoplasmic C-terminal domain (Fig. 1; Palczewski et al., 2000).

Both low-resolution EM structures (Unger et al., 1997) and higher-resolution crystal structures (Palczewski et al., 2000) showed the seven transmembrane helices to be of various lengths tilted at various angles with respect to each other and the plane of the membrane. The crystal structures in particular have revealed that the individual helices can contain kinks, tightenings, and