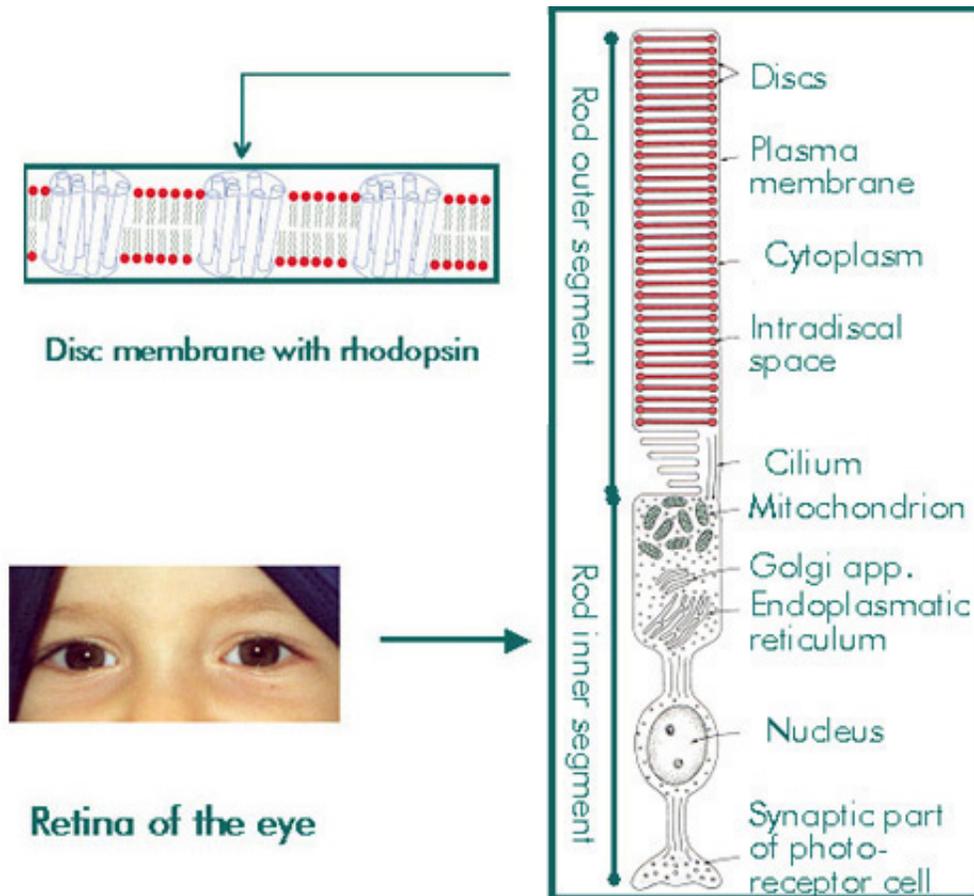


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## Rhodopsin - a G-protein binding receptor in the retina of the eye

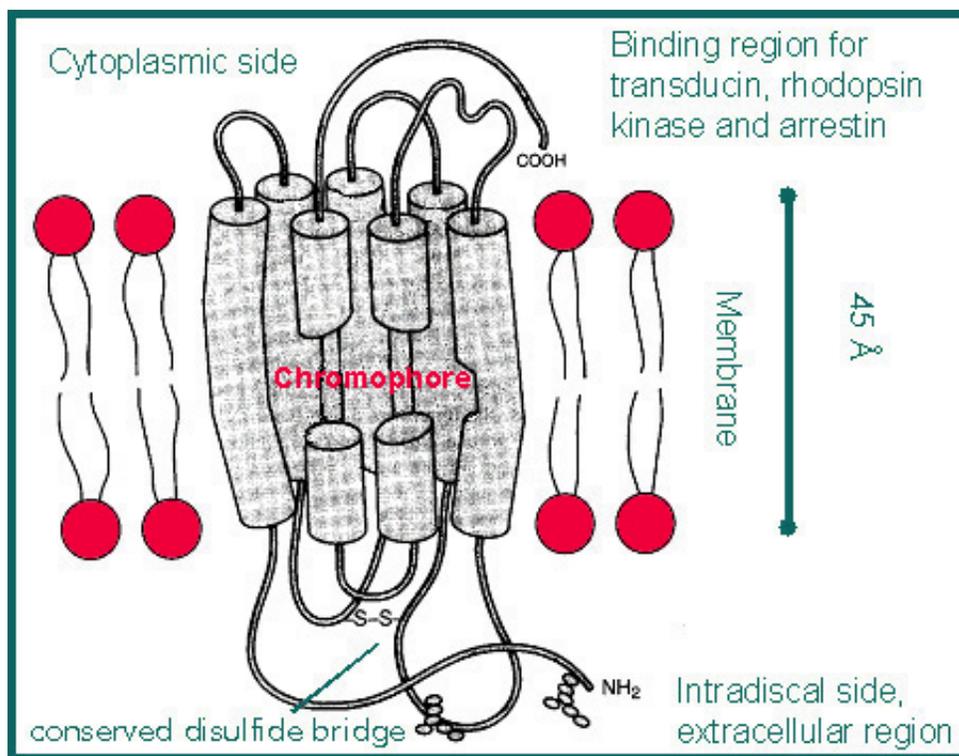
Rhodopsin is a membrane protein in the retina of the eye. There in rods and cones different visual pigments are responsible for vision. Rhodopsin, located in the disc membranes of the rod outer segments, is the pigment which enables us to see dim light.



Light induces a conformational change of rhodopsin's chromophore 11-cis-retinal. The chromophore, which is located in the center of the protein, isomerizes to the all-trans conformation. This leads to a change in the structure of the whole protein - rhodopsin is activated.

Now it is possible for the G-protein Transducin to bind to rhodopsin. This activates the G-protein itself and so the whole signal transduction cascade for vision is triggered. In the next steps a phosphodiesterase is activated and cGMP-dependent channels in the plasma membrane of the rod outer segment close. The resulting hyperpolarization of the membrane lowers the rate of transmitter release in the synaptic part of the photoreceptor cell. This then triggers downstream responses in bipolar cells.

Rhodopsin is an important member of the large family of G-protein binding receptor. Many different neurotransmitters, hormones and drugs produce their intracellular signalling through the mediation of various G-protein coupled receptors. The binding of a hormone or neurotransmitter causes a change in the structure of the receptor which then activates the G-protein. G-proteins are known to activate adenylate cyclase, to stimulate the opening of K<sup>+</sup> channels in heart cells, or to participate in the phosphoinositide signalling system.



Rhodopsins have amino acid sequence and functional homology with other G-protein coupled receptors, suggesting that all members of this receptor superfamily are structurally related. A common structural feature is the presence of seven hydrophobic transmembrane helices. Conserved features in most G-protein coupled receptors include sites of asparagine-linked glycosylation in the amino-terminal region, one or two palmitate-linked cysteines close to the carboxy-terminal region, a disulfide bridge linking two extracellular loops and serine and threonine phosphorylation sites in the carboxy-terminal region.

## Selected publications

### The Three-dimensional Structure of Bovine Rhodopsin Determined by Electron Cryomicroscopy

Angelika Krebs, Patricia C. Edwards, Claudio Villa, Jade Li, and Gebhard F. X. Schertler

J. Biol. Chem. (2003) 278,(50)

G-protein-coupled receptors are integral membrane proteins that respond to environmental signals and initiate signal transduction pathways, which activate cellular processes. Rhodopsin, a well known member of the G-protein-coupled receptor family, is located in the disk membranes of the rod outer segment, where it is responsible for the visualization of dim light. Rhodopsin is the most extensively studied G-protein-coupled receptor, and knowledge about its structure serves as a template for other related receptors. We have gained detailed structural knowledge from the crystal structure (1), which was solved by x-ray crystallography in 2000 using three-dimensional crystals. Here we report a three-dimensional density map of bovine rhodopsin determined by electron cryomicroscopy of two-dimensional crystals with  $p22_1$  symmetry. The usage of relatively small and disordered crystals made the process of structure determination challenging. Special attention was paid to the extraction of amplitudes and phases, since usable raw data were limited to a maximum tilt of 45°. In the refinement process, an improved unbending procedure was applied. This led to a final resolution of 5.5 Å in the membrane plane and 13 Å perpendicular to it, making our electron density map the most accurate map of a G-protein-coupled receptor currently available by electron microscopy. Most important is the information we gain about the center of the membrane plane and the orientation of the molecule relative to the bilayer. This information cannot be retrieved from the three-dimensional crystals. In our electron density map, all seven transmembrane helices were identified, and their arrangement is in agreement with the arrangement known from the crystal structure (1). In the retinal binding pocket, a density peak adjacent to helix 3 suggests the position of the theb-ionine ring of the chromophore, and in its vicinity several of the bigger amino acids can be identified.

### Projection Structure of Bovine Rhodopsin

### **Characterisation of an improved two-dimensional p22121 crystal from bovine rhodopsin.**

Krebs A, Villa C, Edwards PC, Schertler GF

J Mol Biol 1998 Oct 9;282(5):991-1003

Dialysis of rhodopsin isolated from bovine rod outer segments resulted in the formation of a new two-dimensional crystal form suitable for electron crystallography. The crystals obtained were tubular or single layers and showed p22121 symmetry ( $a=60.6(\pm 0.8)$  Å,  $b=86.3(\pm 1.6)$  Å). For the first time the size and order of the crystals allowed us to take electron diffraction patterns showing spots to a resolution of about 3.5 Å. Images were recorded at liquid nitrogen temperature using a high voltage field emission electron microscope. Out of a large number of images 20 crystalline areas were selected and processed with the MRC image processing software. A projection structure of bovine rhodopsin to 5 Å resolution was calculated using amplitudes and phases extracted from these images. The achieved resolution exceeds the resolution of all previously obtained structures of frog, bovine and squid rhodopsin crystals. In this map small differences are observed compared to the previous maps. Helix 5 seems to be even more highly tilted and between the arc-shaped feature and helix 5 a peak is present suggesting that helix 3 is prolonging this feature towards helix 5. These observations are in agreement with the latest model for the three-dimensional arrangement of rhodopsin. The resolution achieved as well as the availability of electron diffraction data suggest that there is a good possibility to collect data from tilted crystals and calculate an improved three-dimensional structure of rhodopsin.

### **Three-dimensional Structure of an Invertebrate Rhodopsin and Basis for Ordered Alignment in the Photoreceptor Membrane**

Anthony Davies, Brent E. Gowen, Angelika M. Krebs, Gebhard F. X. Schertler, Helen R. Saibil

Journal of Molecular Biology 314, 3, 2001 pp. 455-463

Invertebrate rhodopsins activate a G-protein signalling pathway in microvillar photoreceptors. In contrast to the transducin-cyclic GMP phosphodiesterase pathway found in vertebrate rods and cones, visual transduction in cephalopod (squid, octopus, cuttlefish) invertebrates is signalled via Gq and phospholipase C. Squid rhodopsin contains the conserved residues of the G-protein coupled receptor (GPCR) family, but has only 35% identity with mammalian rhodopsins. Unlike vertebrate rhodopsins, cephalopod rhodopsin is arranged in an ordered lattice in the photoreceptor membranes. This organization confers sensitivity to the plane of polarized light and also provides the optimal orientation of the linear retinal chromophores in the cylindrical microvillar membranes for light capture. Two-dimensional crystals of squid rhodopsin show a rectilinear arrangement that is likely to be related to the alignment of rhodopsins *in vivo*. Here, we present a three-dimensional structure of squid rhodopsin determined by cryo-electron microscopy of two-dimensional crystals. Docking the atomic structure of bovine rhodopsin into the squid density map shows that the helix packing and extracellular plug structure are conserved. In addition, there are two novel structural features revealed by our map. The linear lattice contact appears to be made by the transverse C-terminal helix lying on the cytoplasmic surface of the membrane. Also at the cytoplasmic surface, additional density may correspond to a helix 5-6 loop insertion found in most GPCRs relative to vertebrate rhodopsins. The similarity supports the conservation in structure of rhodopsins (and other G-protein-coupled receptors) from phylogenetically distant organisms. The map provides the first indication of the structural basis for rhodopsin alignment in the microvillar membrane.

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