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Rhodopsin

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Rhodopsin is the primary photoreceptor molecule of vision. Light striking a rhodopsin molecule in a photoreceptor cell of the retina is converted into a biochemical signal by a photochemical reaction. The signal is processed by other cells in the retina and sent to the brain. Two general types of photoreceptor cells exist in the vertebrate retina and are named according to their characteristic shapes: (1) rods and (2) cones. Rod cells are responsible for dim-light vision, whereas cone cells are responsible for bright-light color vision. Photoreceptor rod cells contain rhodopsin. Cone cells, responsible for bright-light and color vision in vertebrates, contain iodopsins, also known as *cone pigments* or *color vision pigments*. The photoreceptor cells of invertebrate species also contain rhodopsin, even though the anatomy of invertebrate vision varies dramatically from that of the vertebrate visual system.

All visual pigments consist of an opsin protein plus a chromophore. The chromophore is a cofactor, which is linked covalently via a Schiff base bond to a specific lysine amino acid residue of the opsin protein. One of two retinoids serves as the chromophore for nearly all visual pigments. The chromophore in most vertebrate pigments is the aldehyde of vitamin A, 11-*cis*-retinal. The chromophore in some fishes and amphibians is the aldehyde of vitamin A₂, 11-*cis*-3-dehydroretinal, which contains an additional carbon-carbon double bond in the β-ionone ring (Figure 1).

Photoisomerization of the 11-*cis* to all-*trans* form of the chromophore is the primary event in visual signal transduction, and it is the only light-dependent step. The absorption of a photon, a quantum of energy, by rhodopsin causes the photoisomerization. Although rhodopsin can absorb a fairly wide range of light energies, green light is most effective in activating rhodopsin. The wavelength of light that is maximally absorbed (λ_{\max} value) is 500 nm (Figure 2). Upon photoisomerization of the chromophore, the pigment is converted to a spectral form called *metarhodopsin II* (MII) with a λ_{\max} value of 380 nm. The MII intermediate is characterized by a deprotonated Schiff base chromophore linkage. MII is the active form of the receptor, which is able to transmit a biochemical signal as described following.

Rhodopsin is found primarily within the disk membrane of the rod cell (Figure 3). The amino terminus of rhodopsin is extracellular, whereas the carboxyl terminus is intracellular, or cytoplasmic. The protein spans the membrane bilayer seven times (Figure 4) and the resulting seven transmembrane helices of rhodopsin fold to form a pocket to accommodate the retinal chromophore (Figure 5). The chromophore-binding pocket resides in the membrane-embedded domain of the protein. A lysine residue, which acts as the linkage site for the chromophore, is conserved within the seventh transmembrane segment in all visual pigments. In addition, a pair of highly conserved cysteine residues is found on the extracellular surface and may form a stabilizing disulfide bond. In many pigments a carboxylic acid residue, which acts as the counterion to the positively charged protonated Schiff base, is conserved within the third transmembrane segment. A cluster of serine and threonine residues is found in the carboxyl-terminal tails of most visual pigments. These sites become phosphorylated in response to light and provide a mechanism to attenuate the light response, because a phosphorylated rhodopsin is prevented from transmitting its biochemical signal.

Visual pigments, including rhodopsin, are members of a large family of G protein-coupled receptors. Bovine rhodopsin was the first G protein-coupled receptor to be sequenced by amino acid sequencing, the first to be cloned, and the first for which a high-resolution radiographic crystal structure has been reported. Bovine rhodopsin is 348 amino acid residues in length and is identical to human rhodopsin at all but 23 positions. The cloning of a β-adrenergic hormone receptor led to the identification of the structural homologies that now define the superfamily of G protein-coupled receptors. Molecular cloning has identified several hundred different but related G protein-coupled receptors. All G protein-coupled receptors reside in cell membranes and consist of seven hydrophobic membrane-spanning domains, and they are all involved in the general process of signal transduction. The signal transduction may involve sensory processes such as vision or olfaction. However, the receptors responsible for synaptic transmission of a neural signal, or for sensitivity to various hormonal signals are also members of the G protein-coupled receptor family.

The receptors become activated, either by light in the case of rhodopsin or by binding to an appropriate agonist ligand such as a neurotransmitter or hormone. The activated receptor interacts biochemically with another class of proteins, called *guanine nucleotide-binding regulatory proteins*, or *G proteins*. The G protein transduces the biochemical signal to some cellular effector molecule, which ultimately affects cellular function, growth, or metabolism. Examples of cellular effector enzymes include adenylyl cyclase, which produces cyclic adenosine monophosphate (cAMP), or phospholipase C, which produces phosphatidyl inositides. Some G proteins can interact directly with ion channels in the cell membrane.

The molecular cloning of opsins from a variety of species has allowed detailed comparisons of visual pigments based on their structural, spectral, and biochemical properties. Pigment genes have been classified phylogenetically and models of pigment evolution have been proposed. The homology in the opsin family of genes indicates that divergent evolution occurred from a single precursor retinal-binding protein to form long- and short-wavelength absorbing prototypes. The long-wavelength prototype diverged to form red and green pigments. The short-wavelength prototype then diverged to form a blue pigment and the family of rhodopsins and rhodopsin-like green pigments.

1. Spectral tuning of rhodopsin and cone visual pigments

Humans possess trichromatic color vision, or trichromacy. Most people can match any given reference color by combining the three primary colors. The three primary colors for additive color mixtures are red, green, and blue. In addition to rod cells, which contain rhodopsin, the retina contains three classes of cone photoreceptor cells. Each class of cone cell is sensitive to a specific wavelength of light. At the molecular level, human trichromatic color vision requires the presence of three cone pigments with broad overlapping spectral absorption. Each specific cone class contains only one type of photoreceptor molecule. The three types of cone photoreceptor molecules (red, green, and blue) are homologues of rhodopsin. The amino acid sequences of these opsins are about 40% identical to that of human rhodopsin. The green and red opsins are about 96% identical to each other and about 43% identical to the blue opsin. The spectral properties of human cone pigments have been studied by a variety of techniques including psychophysical color matching and microspectrophotometry. In addition, the molecular cloning of the cone pigment genes has allowed the study of the molecular mechanism of spectral tuning and the molecular genetics of color vision.

All pigments are tuned to a characteristic wavelength of maximal absorption (λ_{\max}). Rhodopsin and the three cone pigments all use the same chromophore, 11-*cis*-retinal. Despite the fact that retinal is the universal chromophore, the λ_{\max} values of visual pigments span the visible spectrum, which ranges from about 400 nm (violet) to 600 nm (deep red). Thus a single chromophore allows all visible wavelengths of light to be detected. A spectral tuning mechanism exists so that a particular opsin protein can modulate the absorption spectrum of its retinylidene chromophore. Spectral tuning is possible, because specific amino acid side chains of each opsin can interact with the chromophore and shift its λ_{\max} value. For example, the human green and red opsin proteins display only 15 differences among their 364 amino acid residues. Of these 15 differences, seven amino acid changes are responsible for the observed 30 nm spectral shift in going from the λ_{\max} value of the green to that of the red pigment. Most of this shift is caused by three amino acid side chains that contain hydroxyl groups: (1) tyrosine, (2) serine, and (3) threonine.

Genetic variations in color vision may result from a mutation in one of the genes encoding a cone opsin. If the amino acid change affects spectral tuning in one of the cone pigments, then one of the cone types will contain a pigment with an anomalous absorption spectrum. Individuals with this genetic variation are called *anomalous trichromats*. The most common type of anomalous trichromacy is called red-green "color blindness." Red-green color vision variations affect males predominantly, because the genes for the red and green opsin genes are found on the X-chromosome. Severe color vision defects may result from complete deficiencies of one or more of the three cone opsin genes. Individuals who lack a functional red or green photoreceptor are called *dichromats*.

2. The biochemical cascade of vertebrate vision

Photoisomerization of retinal activates rhodopsin, allowing it to interact with a specific G protein. The rod cell G protein, transducin, transmits a biochemical signal from rhodopsin to a cellular effector molecule. Photoactivated rhodopsin catalyzes the exchange of guanosine 5'-diphosphate (GDP) for guanosine 5'-triphosphate (GTP) by transducin molecules. A single activated rhodopsin can activate catalytically up to 500 transducin molecules. The activated transducin, with GTP in its nucleotide-binding pocket, then transmits a chemical signal to the effector molecule in the signaling cascade. The effector molecule in the vertebrate visual system is the enzyme guanosine 3':5' cyclic guanosine monophosphate (cGMP) phosphodiesterase. A single transducin molecule activates a single phosphodiesterase molecule. However, each phosphodiesterase can catalyze the hydrolysis of up to 3000 cGMP molecules to GMP molecules per second. Thus the biochemical amplification is as much as six orders of magnitude at the molecular level. The lowered levels of cGMP in the rod cell cause plasma membrane cation channels to close. A single photon causing retinal isomerization can affect the conductance of approximately 1000 plasma membrane cation channels.

Because the plasma membrane is selectively permeable to ions, which are electrically charged, an electrical potential difference exists between the inside and the outside of the rod cell. The potential increases as cation channels are closed and the influx of sodium and calcium ions, which carry positive charge, is slowed. The result is that the rod cell becomes hyperpolarized in response to light. The increase in potential varies proportionally with the strength of the light signal. The change in membrane potential is sent as an electrical signal from the plasma membrane to the synaptic terminal of the rod cell, where it is transmitted to other specialized cells of the retina.

A properly dark-adapted rod cell can detect a single photon. This extreme sensitivity is possible in part because of two important features of the visual system: (1) the stability of rhodopsin in darkness to thermal activation, and (2) the high degree of signal amplification by the biochemical cascade of vision. It has been estimated that the spontaneous thermal isomerization of 11-*cis*-retinal in rhodopsin in darkness only takes place roughly once in 300 to 1000 years. In contrast (as presented previously), a single photon can theoretically cause as many as 1000 cation channels in a rod cell membrane to close.

The light signal is turned off by a number of biochemical mechanisms. Light-activated rhodopsin becomes phosphorylated by a specific rhodopsin kinase enzyme. The phosphorylated form of rhodopsin can no longer interact with transducin. The active GTP-bound form of transducin has an intrinsic enzymatic GTP hydrolysis activity. Over time the bound GTP is converted to GDP, and transducin returns to its inactive state. In addition, intracellular calcium levels drop after the cation channel of the rod cell closes. A fall in intracellular calcium concentration mediates photoreceptor cell recovery and adaptation. The process of adaptation allows the sensitivity of the retina to adjust based on the level of light in a visual scene. Adaptation is extremely important for a useful visual system, because the magnitude of light varies widely in the environment. For example, bright sunlight and dim starlight differ in luminance by at least several orders of magnitude.

3. Mutations in the gene for human rhodopsin may cause disease

Retinitis pigmentosa is a group of hereditary progressive blinding diseases with variable clinical presentations. One form of the disease, autosomal dominant retinitis pigmentosa (ADRP), was linked to a mutation in the gene for rhodopsin. More than 60 different rhodopsin gene mutations have been reported in patients with ADRP. The mutations reported would result in alterations in all domains of rhodopsin: extracellular, membrane-embedded, and cytoplasmic. ADRP is characterized by a progressive death of rod, and sometimes of cone cells, resulting in gradual vision loss. The molecular pathophysiology of ADRP, namely how a defect in rhodopsin leads to rod cell death, remains to be fully elucidated.

4. See also

[Photoreceptors and photoreceptor dysfunctions](#)

[Visual transduction](#)

[Visual adaptation](#)

[Retina, vertebrate](#)

[Retinitis pigmentosa](#)

[Visual transduction](#)

[Color vision](#)

5. Further reading

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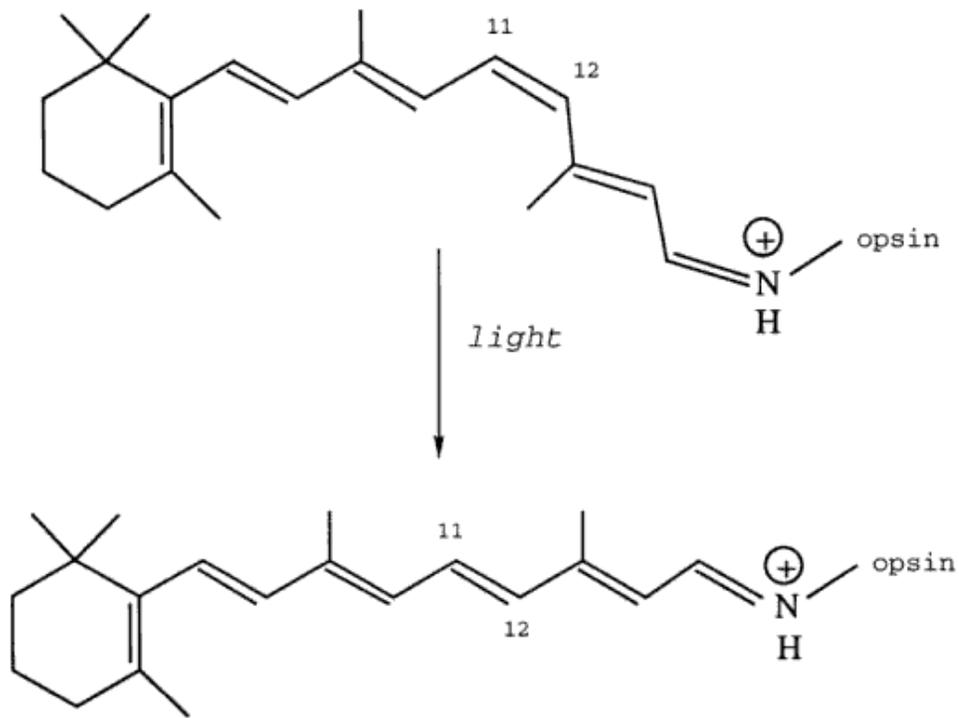
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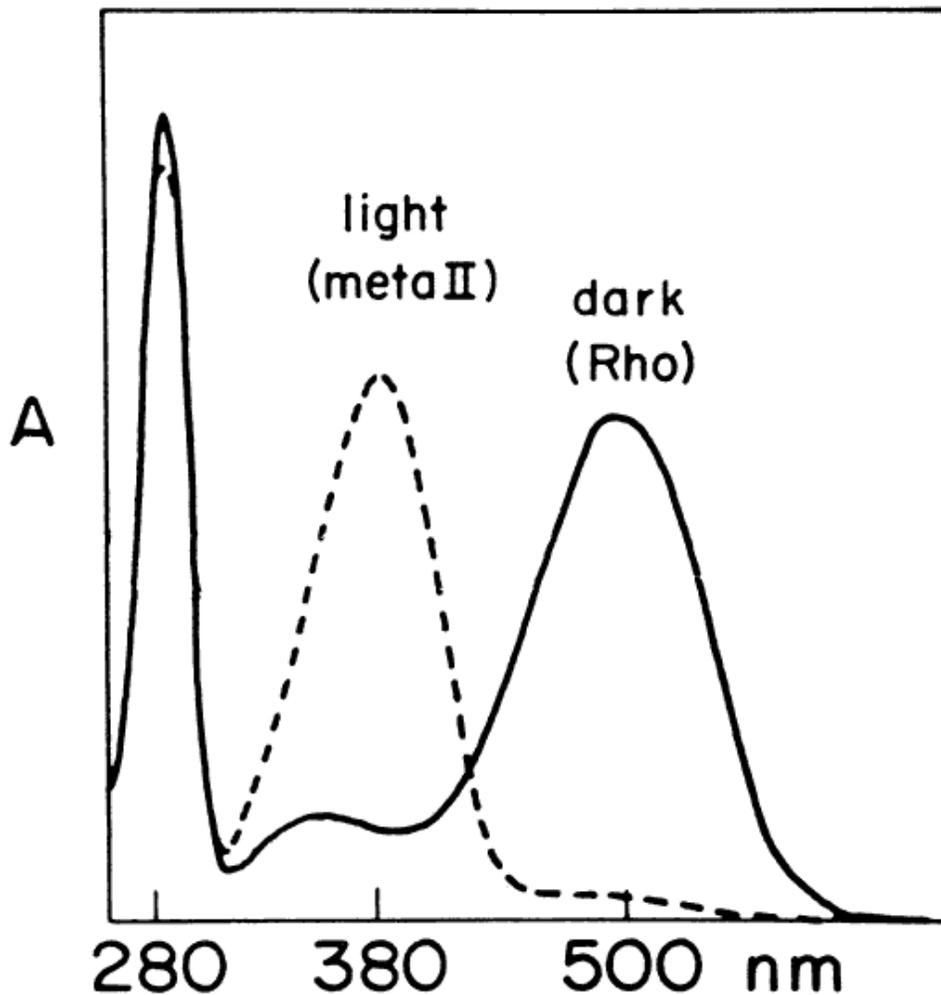
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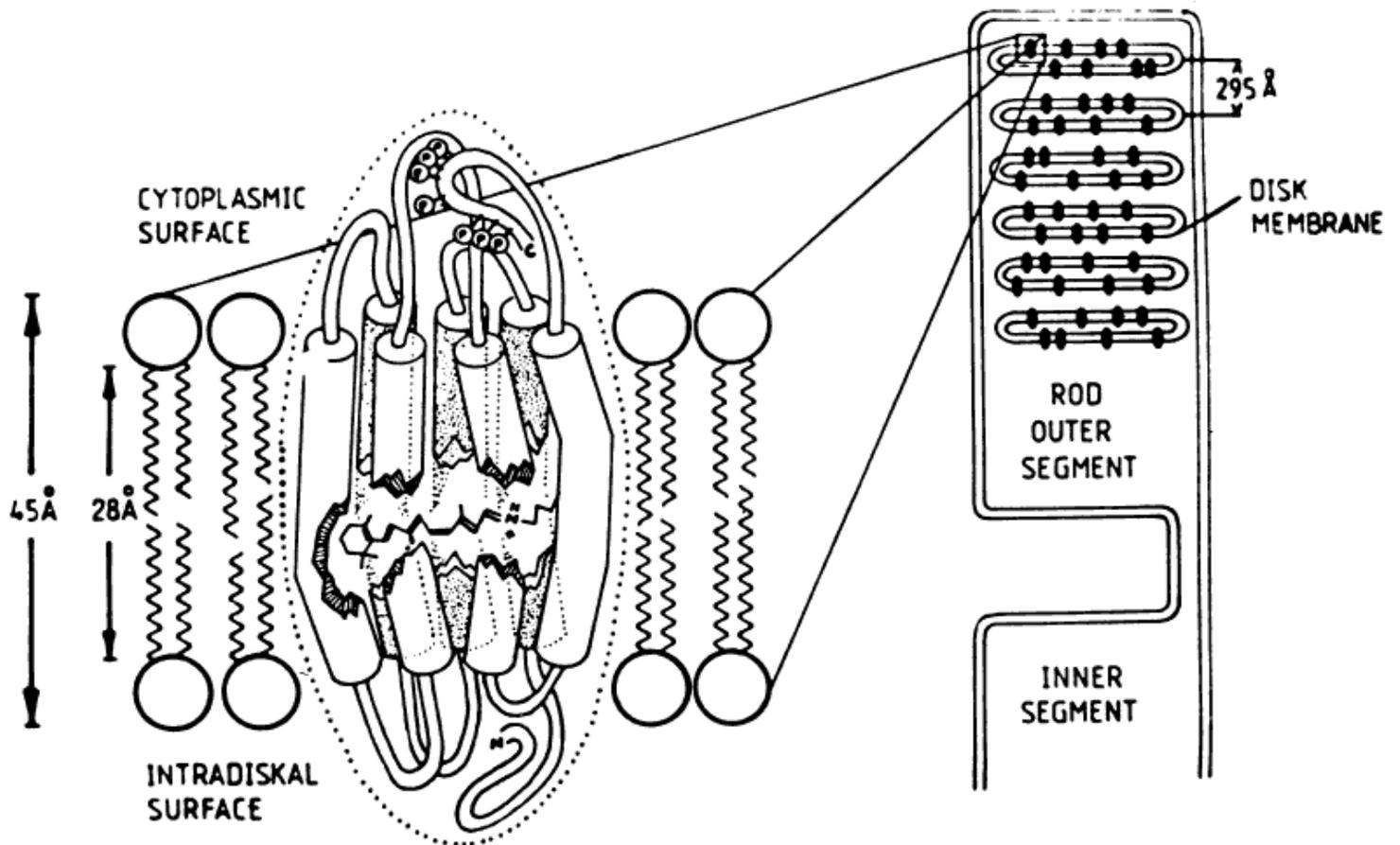
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Figure 1. Photoisomerization of 11-*cis*-retinal to all-*trans*-retinal is the only light-dependent event in vision. Vertebrate visual pigments contain one of two chromophores, vitamin A aldehyde (11-*cis*-retinal, shown here) or vitamin A2 aldehyde (11-*cis*-3-dehydroretinal), which contains an additional carbon-carbon double bond in the β -ionone ring. The chromophore is covalently linked as a cofactor to a specific opsin lysine aminolmax acid residue via a protonated Schiff base bond.



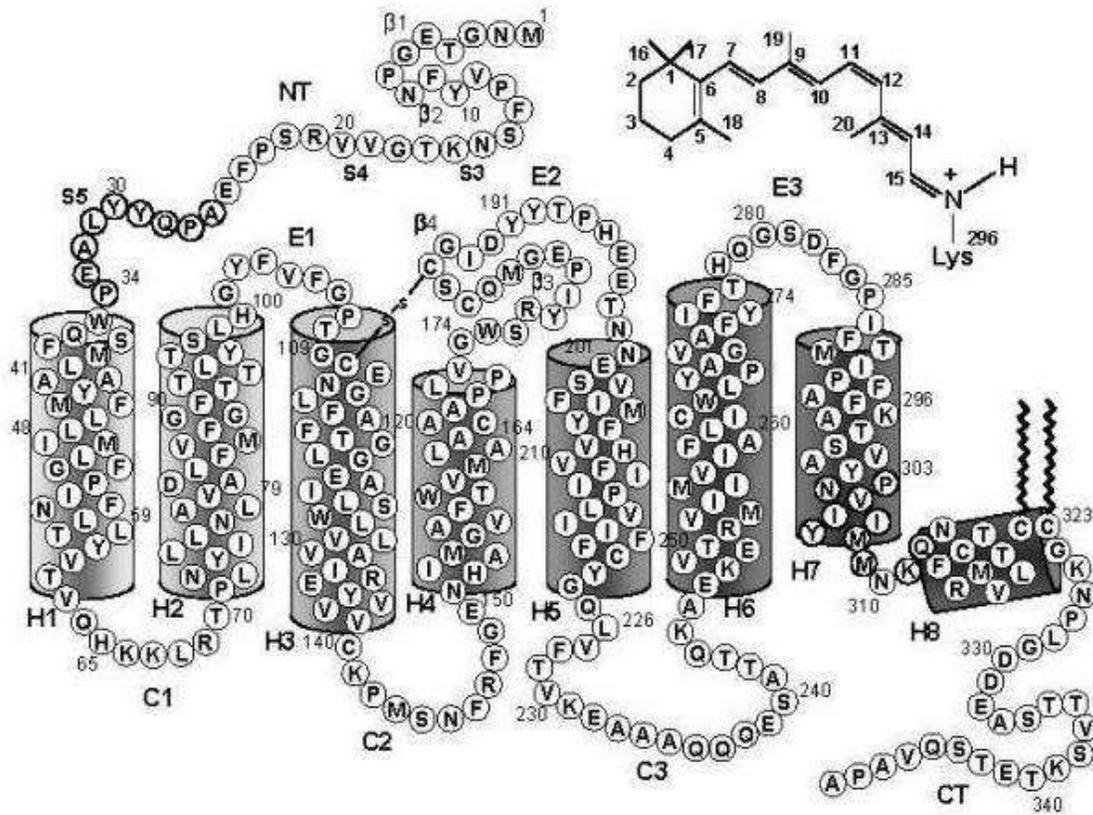
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Figure 2. An ultraviolet-visible absorption spectrum of purified bovine rhodopsin shows a characteristic broad visible absorbance with a λ_{max} value of 500 nm. The 280 nm peak represents the opsin protein component. After exposure to light, the pigment is converted to a peak with a λ_{max} value of 380 nm characteristic of metarhodopsin II. This is the active form of the receptor that interacts with the rod cell G protein, transducin.



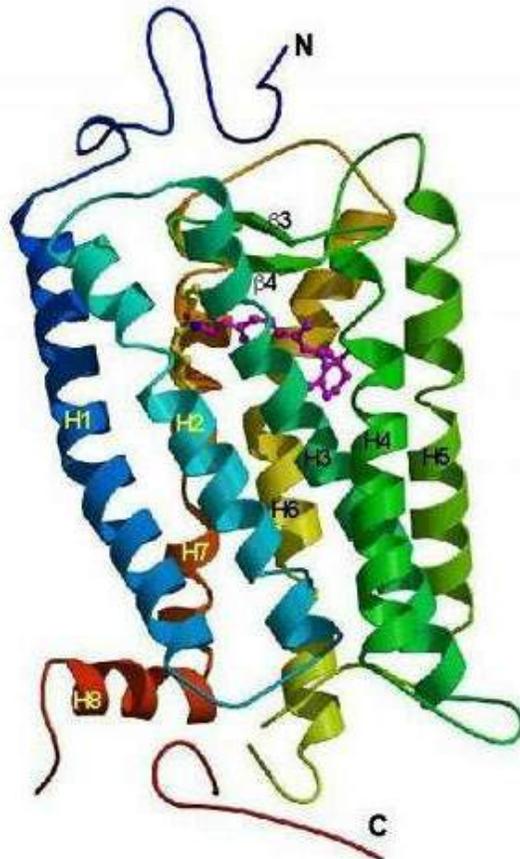
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Figure 3. A schematic representation of bovine rhodopsin within the bilayer of the disk membrane. The seven putative transmembrane helices form a binding pocket for the retinal chromophore. The rod cell consists of an inner segment and an outer segment. The outer segment contains a stack of disk membranes, which are highly enriched in rhodopsin. Other proteins of the biochemical cascade of the vertebrate visual system, including transducin, reside in the cytoplasmic space.



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Figure 4. A secondary structure diagram of bovine rhodopsin. Amino acid residues are depicted in single-letter code. The amino-terminal tail and extracellular domain is toward the top and the carboxyl-terminal tail and cytoplasmic domain is toward the bottom. Transmembrane α -helical segments (H1 to H7) and the cationic amphipathic helix H8 are shown in cylinders. *Inset:* The structure of the retinylidene chromophore. Carbon atoms are numbered 1 through 20.



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Figure 5. A molecular graphics ribbon diagram of rhodopsin prepared from the 2.8 Å crystal structure coordinates. The amino terminus (*N*) and extracellular (or intradiscal) surface is toward the top of the figure and the carboxyl terminus (*C*) and intracellular (or cytoplasmic) surface is toward the bottom. Seven transmembrane segments (*H1 to H7*), which are characteristic of GPCRs, are shown. The transmembrane segments are tilted with respect to the presumed plane of the membrane bilayer. They are generally α -helical but they contain significant kinks and irregularities.

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