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The Biomolecular Events Underlying Mammalian Vision

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Abstract

This literature review examines the biochemical mechanisms underlying rhodopsin activation, transducin coupling, and signal termination in phototransduction. Rhodopsin, a rod cell G-Protein Coupled Receptor (GPCR), undergoes conformational changes upon 11-*cis*-retinal chromophore isomerization, leading to the activation of transducin (G_t) and subsequent downstream signaling. Structural studies—including X-ray crystallography, time resolved serial femtosecond crystallography, and cryogenic electron microscopy—have provided insights into the transitions between inactive and active rhodopsin states and the binding interface between rhodopsin and transducin.

This review synthesizes recent findings on the molecular basis of transducin binding, including key conformational shifts (at the residual and macromolecule level) in rhodopsin's transmembrane helices that propagate to the cytoplasmic face. Additionally,

the role of rhodopsin kinase (GRK1) and arrestin in signal termination and receptor desensitization is explored. Despite significant advances, gaps remain in understanding the precise mechanism of transducin translocation.

By integrating structural and biochemical perspectives, this review highlights current advancements in rhodopsin-mediated phototransduction. In doing so, it provides key insights into the biochemical framework for rhodopsin-transducin mediated signal transduction, with implications for understanding broader GPCR signaling mechanisms.

I. Introduction

One of the key features of a *living organism* is its ability to appropriately respond to stimuli. In order to respond to stimuli, though, living organisms must first be able to detect or *sense* these stimuli. Sensory perception can be broadly categorized as *general* or *special*. The *general senses*–touch, pain, temperature, pressure, vibration, and proprioception–are reactive and distributed throughout the body, providing continuous feedback on physical conditions. In contrast, *special senses*–vision, hearing, taste, smell, and balance–are predictive, localized to specific sense organs, and reliant on specific receptors to process complex stimuli.

Fundamentally, sensation is a biochemical process. The biochemical receptors that comprise the sensory system fall into two categories: ionotropic and metabotropic. Ionotropic receptors, also known as ligand-gated ion channels, rely directly on the flow of ions to cause hyperpolarization/depolarization of the cell membrane. For example, the nicotinic acetylcholine receptor (found on skeletal muscle fibers) is an ionotropic ligand-gated Na^+ channel; upon binding of two acetylcholine molecules (the ligand) to

the receptor, the channel's permeability to sodium increases, causing a rapid efflux of Na^+ ions into the skeletal muscle, depolarizing it and ultimately causing the muscle to contract. On the other hand, metabotropic receptors rely on activating second messenger systems (e.g. cyclic AMP, cyclic GMP) to initiate signaling cascades that ultimately affect the metabolic activity and overall function of the cell. The two main types of these receptors are receptor-tyrosine kinases (RTKs) and G-protein coupled receptors (GPCRs), the latter of which are essential for sensory perception.[1]

GPCRs are integral proteins embedded in the cellular plasma membrane, and they form the molecular framework for transmission of intercellular information. Although GPCRs have many diverse roles (e.g. the adrenergic receptors control sympathetic tone while the dopaminergic receptors reward behavior), GPCRs have a highly conserved prototypical structure: they pass through the plasma membrane 7 times and are thus also known as 7-transmembrane domain (7TM) receptors. GPCRs are coupled to G-proteins, which are heterotrimeric intracellular signaling proteins whose activation state is controlled by GTP (on state) and GDP (off state).[2]

Vision is one of the most developed special senses in humans. The proteins responsible for vision are GPCRs called *opsins*. The *S*-opsin, *M*-opsin, and *L*-opsin are found in the ocular cone cells and are responsible for color vision. The GPCR rhodopsin is found in rod cells and is responsible for dim light vision.

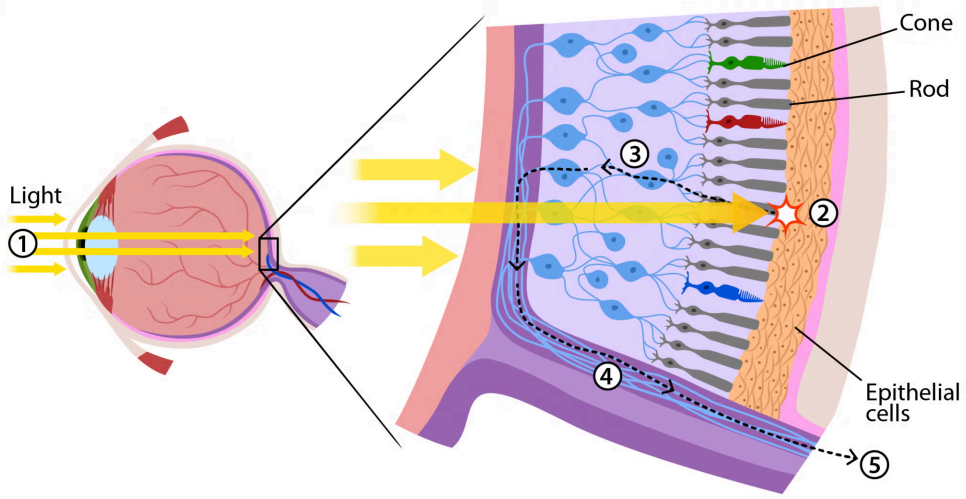

Figure 1. A schematic of the human eye. 1. Light moves through the lens towards the retina at the back of the eye. 2. Incident photons hit the outer segment of the rods and cones and activate the initiation of the opsins. 3. Opsins generate an intracellular signal that is then transferred to neurons known as retinal ganglion cells (RGCs). 4. The signal (an action potential) moves through the RGCs into the optic nerve. 5. The action potential propagates down the active nerve into the occipital lobe, where the signals will be processed into an image.[3]

Due to its high expression and homogeneous distribution in rod cells, rhodopsin has been an easily accessible target for studying phototransduction–the process through which light information is converted into an image by the brain. Rhodopsin is a prototypical GPCR with a 7TM structure. The chromophore 11-*cis*-retinal, a vitamin A derivative, is attached to rhodopsin and is the ligand which undergoes isomerization upon photon absorption. The isomerization of 11-*cis*-retinal to all-*trans*-retinal leads to

changes in the molecular structure of rhodopsin that ultimately lead to translocation of transducin–the G-protein associated with rhodopsin.[4] This activates the α subunit of transducin (Tα) (by causing GDP/GTP exchange in the α subunit), initiating the signaling cascade associated with steps 3-5 in **Figure 1.** Specifically, active Tα binds to and activates phosphodiesterase 6, an enzyme responsible for catalyzing the hydrolysis of cGMP into GMP. A lower cGMP concentration leads to closure of cGMP-gated Na^+/Ca^{2+} channels, causing rod cell hyperpolarization. The signal is then transmitted down the visual pathway. The phototransduction pathway can be seen in **Figure 2.**

To prevent continuous activation of rhodopsin and return the protein to its initial state, rhodopsin signaling is mediated by rhodopsin kinase (GRK1) and arrestin. These regulatory proteins ensure proper signal resolution and prevent prolonged or excessive activation. Once rhodopsin has been activated by photon absorption, GRK1 phosphorylates its cytoplasmic tail, creating binding sites for arrestin. Subsequent binding of arrestin creates steric hindrance that limits further interaction between transducin and rhodopsin. This effectively shuts down the signaling cascade.[5] Additionally, the isomerized trans chromophore must be removed and replaced with the inactive cis retinal. This is accomplished through a series of enzyme catalyzed redox reactions by the retinal epithelium enzymes retinol dehydrogenase (RDH) 8 and 12.[6]

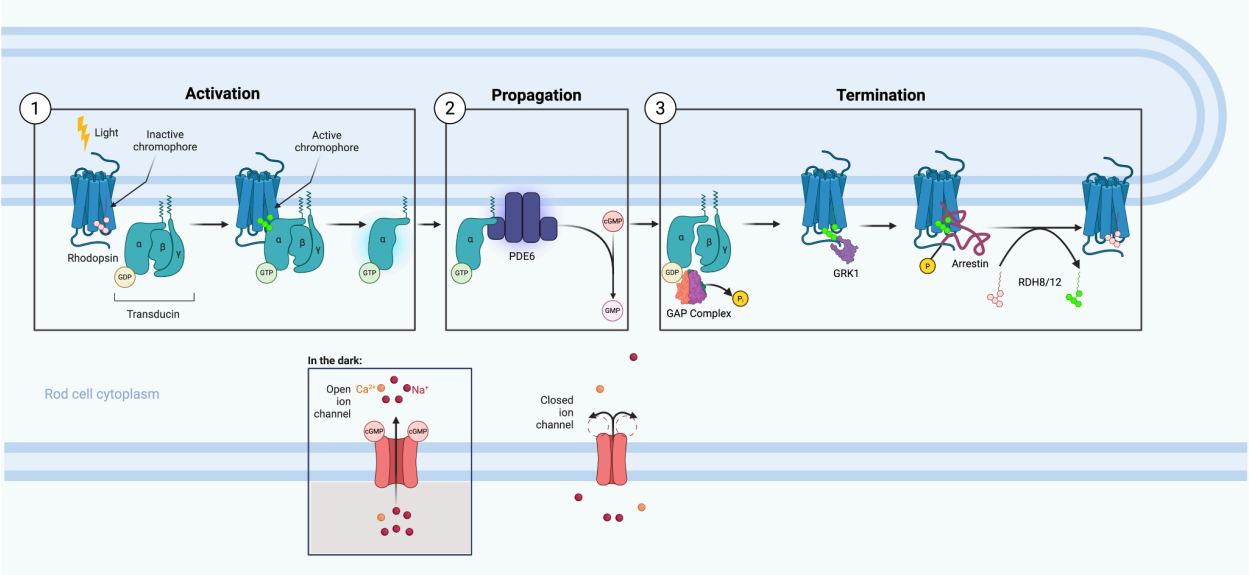

Figure 2. A schematic representation of the phototransduction pathway.

The goal of this review is to examine and coherently synthesize the molecular mechanisms underlying phototransduction by (1) elucidating the biochemical mechanism of retinal isomerization, (2) analyzing the conformational changes in rhodopsin that facilitate transducin binding, and (3) detailing the structural and biochemical interactions governing transducin activation. Additionally, this review will (4) explore the molecular basis of rhodopsin signaling termination via rhodopsin kinase and arrestin. Emphasis will be placed on structural studies, biophysical techniques, and experimental approaches used to dissect these molecular processes.

II. Molecular Components of Phototransduction

At the molecular level, the key players involved in activation of the phototransduction pathway are the GPCR rhodopsin, its coupled G-protein transducin, and the chromophore 11-*cis*-retinal. The second messenger systems affected by

photoactivation involve phosphodiesterase 6 and cGMP gated Ca^{2+} channels, the specific molecular structures of which are not essential to this review. Deactivation of rhodopsin involves rhodopsin kinase 1 (GRK1) and arrestin as well as the retinal dehydrogenases 8 and 12, which restore the 11-*cis*-retinal chromophore from its *trans* counterpart.

Structure of Rhodopsin

The three-dimensional crystal structure of inactive rhodopsin was resolved in a landmark 2000 at 2.8 Å resolution using X-Ray Crystallography (XRC).[8] This study provided the first high-resolution structural insights into mammalian GPCRs. Rhodopsin is a prototypical GPCR with 7 transmembrane α-helices (TM1-TM7) which are connected by 3 cytoplasmic (C-I, C-II, C-III) and 3 extracellular (E-I, E-II, E-III) loops (**Figure 3).** The C-terminal cytoplasmic tails serves as a regulatory domain for phosphorylation by rhodopsin kinase and subsequent arrestin binding, steps which are critical for rhodopsin deactivation.

The inactive state of rhodopsin is stabilized by key intramolecular interactions. These interactions help maintain rhodopsin in its rigid inactive form. A Cys110-Cys187 disulfide bridge stabilizes the extracellular E-II loop, ensuring correct protein folding and preserving the structural integrity of the ligand-binding pocket.[10, 11] A Glu113-Lys296 salt bridge further stabilizes rhodopsin's inactive state, and the Glu113 residue serves as a counterion stabilizing the protonated Schiff base (Lys296).[8,10]

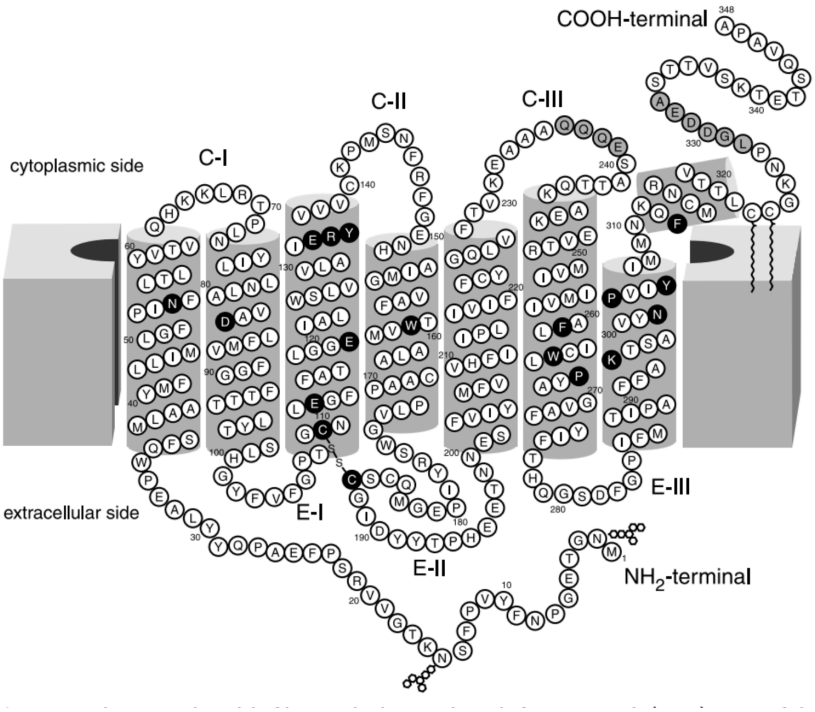

Figure 3. A 2-D representation of rhodopsin's tertiary structure.. Each cylinder corresponds to a transmembrane helix, numbered 1-7 from left to right, and the circles indicate amino acid residues using the standard 1-letter code.[8]

The Retinal Chromophore

The 11-*cis*-retinal chromophore serves as the primary photoreceptive ligand, absorbing incident photons and undergoing a photoisomerization at its 11th carbon into all-*trans*-retinal (**Figure 4)**.[8] The chromophore is extremely light sensitive and can isomerize through absorbing the energy from just 5 photons.[8] Upon the chromophore's isomerization, changes in intermolecular interactions around the ligand-binding pocket propagate through rhodopsin, resulting in its activation. Gruhl et al. (2023) utilized

time-resolved serial femtosecond crystallography (TR-SFC) to capture these ultrafast conformational transitions, showing that bonding interactions around the chromophore shift within femtoseconds of photon absorption.[10] These structural rearrangements occur prior to full activation of rhodopsin, revealing early intermediates that had previously been inaccessible to slower-resolution techniques. The study offers detailed insight into how interaction-level changes within the ligand-binding pocket initiate downstream phototransduction.

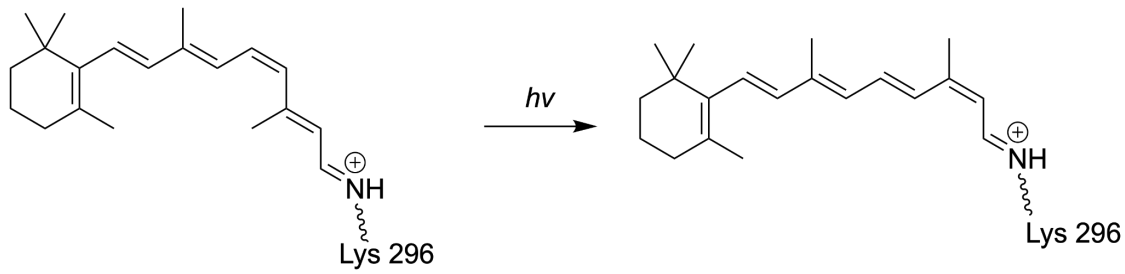

Figure 4. Isomerization reaction showing the conversion of 11-*cis*-retinal to all-*trans*-retinal with their protonated Schiff-base linkages to Lys 296.

III. Activation of Rhodopsin

Following the absorption of a minimum of 5 photons, the 11-*cis*-retinal spontaneously isomerizes into all-*trans*-retinal **(Figure 4).** This process occurs within femtoseconds and disrupts the electronic and steric equilibrium of the chromophore-binding pocket, initiating a cascade of structural changes that propagate throughout the protein. The Schiff base Lys296 linking the chromophore to the protein

undergoes deprotonation, resulting in significant alterations to the ligand-binding site.[10] This proton transfer is facilitated by Glu113 on TM3, the primary counterion stabilizing the protonated Schiff base in the dark state. Deprotonation of the protonated Schiff base causes destabilization of the intermolecular bonding network around the chromophore.[8,10] Specifically, there is a weakening of interactions between retinal and TM3, the central transmembrane helix, such that the retinal molecule essential strips itself away from the central helix (**Figure 5).**[10] The TM3 region is highly conserved among class A GPCRs (playing an important role in both ligand-binding and G-protein coupling); thus, relaxation of interactions around TM3 serve to prime the receptor for transducin coupling. Moreover, other early structural changes upon retinal photoisomerization include outward tilts of Pro215 and Pro267, located around the middle of TM5 and TM6, increasing kinking and creating a G-protein (transducin) binding pocket.[10]

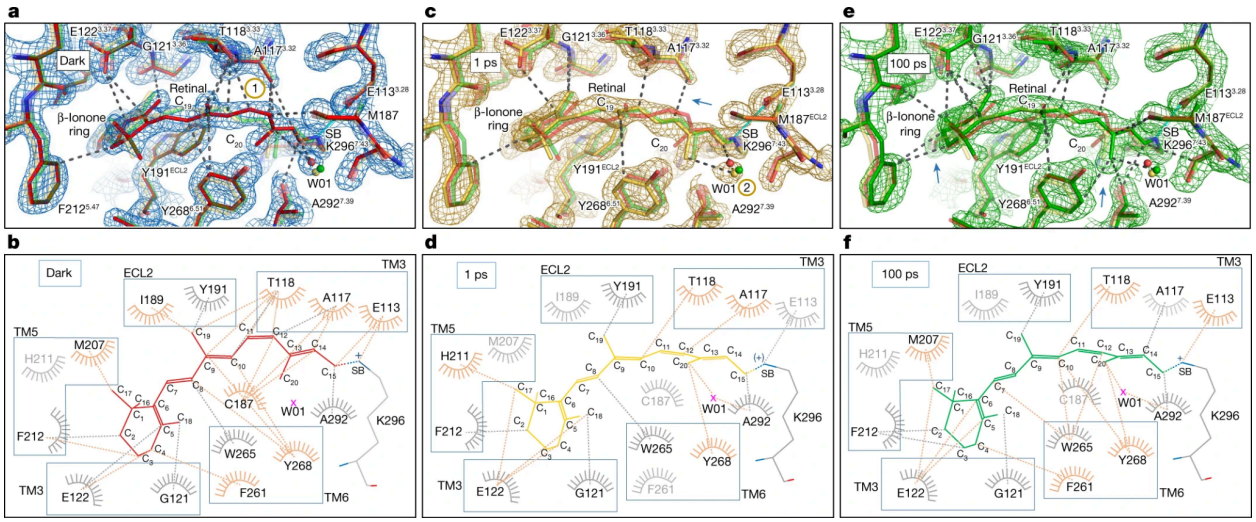

Figure 5. Schematic representation of the residual changes which occur 0, 1ps, and 100ps post photoactivation. Frames a, c, and e show a 3D stick model of the

ligand-binding pocket (in PyMol), while frames b, d, and f show flat interaction plots (in LigPlot). In all frames, red is dark-state rhodopsin, yellow is rhodopsin 1ps after light activation, and green is rhodopsin 100ps after light activation The orange lines indicate new interactions and greyed residue labels indicate loss of interaction. In particular, notice the loss of key interactions between TM3 and the retinal between 0, 1ps and the loss of interactions between Phe212 and Phe262 on TM5 and TM6, respectively, in the same timeframe.[10]

At the molecular level, the most pronounced conformational change following retinal isomerization is the outward displacement of TM6. Using Double Electron-Electron Resonance (DEER), Altenbach et al. (2008) precisely measured this movement, showing that TM6 undergoes an outward shift of approximately 5 Å relative to its position in active rhodopsin (**Figure 6**).[12]

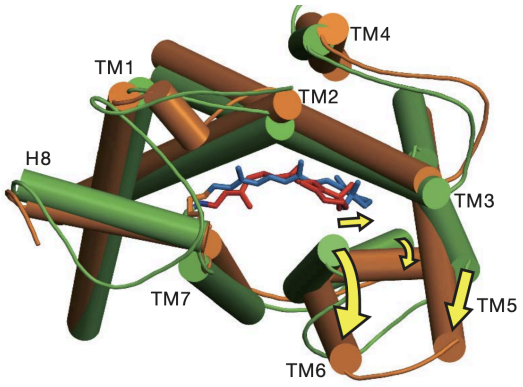

Figure 6. Depiction of the rigid-body tilt of TM6 and slight movement of TM5 following retinal isomerization. (Green = rhodopsin, orange = metarhodopsin II (active state), red = 11-*cis*-retinal, blue = all-*trans*-retinal)[13]

The displacement of TM5 exposes a hydrophobic binding interface that is critical for transducin coupling, marking a key transition into the active Metarhodopsin II state.[13] The cytoplasmic ends of TM5 and TM6 rearrange to form a crevice to accommodate Tα binding, generated largely by changes in residues Phe208, Phe212, and Phe273

located on TM5 and TM6 and displacement of Glu134 and Arg135, disrupting a key salt bridge (**Figure 7**).[13, 8]

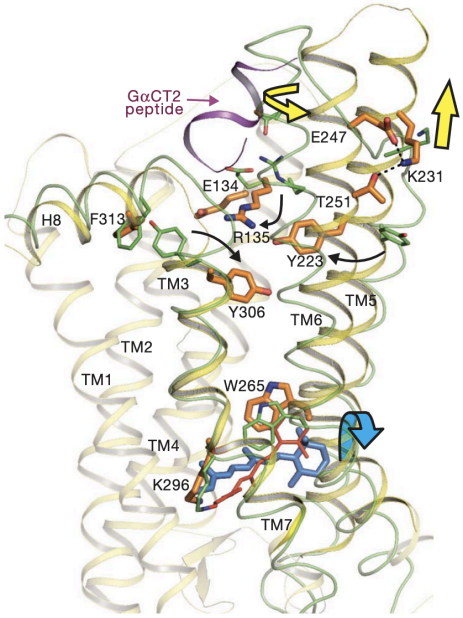

Figure 7. A model illustrating the key steps of rhodopsin activation. Elongation of TM5 and rotation of TM6 is indicated by the yellow arrows, whereas retinal kinking (following isomerization) is indicated by the blue arrow. Together, these movements expose a cytoplasmic binding site in C-III for Tα coupling (purple).[13]

These molecular events collectively drive rhodopsin into its fully active conformation, allowing it to efficiently couple to transducin and initiate downstream signaling. The sequence of conformational shifts, from Schiff base deprotonation to TM6 displacement, represent the fundamental mechanism by which photon absorption is transduced into a biochemical signal.

IV. Transducin Interaction

The interaction between activated rhodopsin (Metarhodopsin II) and the heterotrimeric G-protein transducin occurs through well-defined cytoplasmic binding sites that mediate the exchange of GDP for GTP, a key activation step of Tα (the α subunit of transducin). Covalent crosslinking studies identified residues 310-313 and

343-345 in the cytoplasmic tail of Tα which bind to the third cytoplasmic loop C-III in rhodopsin.[14] Further insights from gain-of-function mutagenesis studies mapped C-II and C-III as functionally significant in transducin binding and activation.[15] Specifically, substitution of amino acids in the C-II and C-III cytoplasmic loops with poly-alanines and subsequent selective reintroduction of native residues revealed that residues adjacent to the transmembrane helices (in the cytoplasmic domain) are crucial for transducin coupling.[15]

High-resolution cryo-electron microscopy studies by Gao et al. (2019) further elucidated the molecular mechanism governing transducin activation.[15] Their analysis showed that the β and γ subunits of transducin function as a "latching switch" for facilitating nucleotide exchange. This stabilization lowers the steric and energy barrier for GDP dissociation, promoting GTP binding and subsequent Tα activation (**Figure 8**).

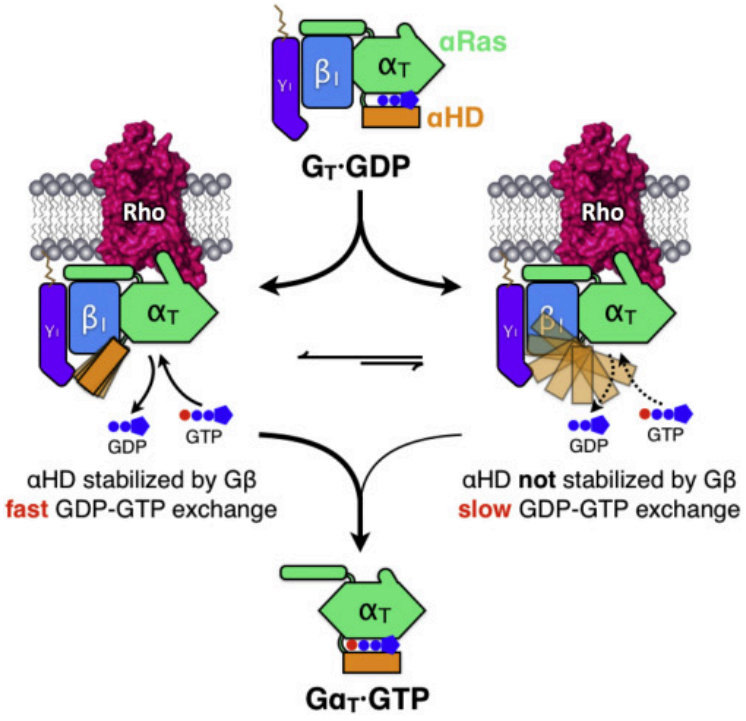

Figure 8. A schematic of the latching switch mechanism. αRas is the GTPase domain of Tα and αHd is the helical domain (part that interacts with Tβ and Tγ). Tβ latches onto αHd and holds it in an open conformation (through electrostatic interactions), exposing the nucleotide binding

pocket. Moreover, the latching mechanism positions αHd in close proximity to αRas, allowing for quick GDP-GTP exchange closure of the exposed binding pocket.[15]

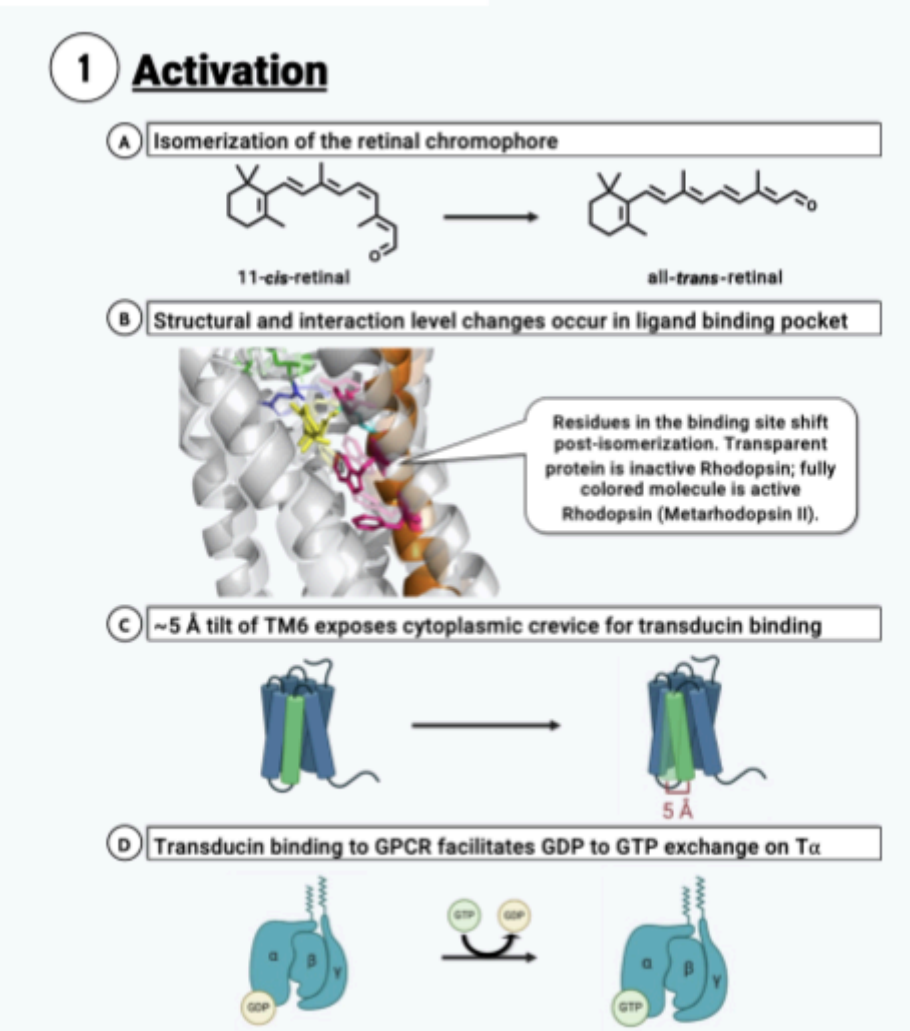

Figure 9. A summary of the steps in the activation phase. Isomerization of the retinal-ligand leads to structural and interaction level changes, which ultimately leads in a helical tilt of TM6, exposing the transducin binding pocket. Once transducin binds, GDP is swapped for GTP, thereby activating Tα.

V. Downstream Signaling Events

Following rhodopsin catalyzed GDP-GTP exchange, activated Tα interacts directly with tetrameric cGMP phosphodiesterase (PDE6) by binding its inhibitory PDEγ

subunit. This “trapping mechanism” stabilizes PDEγ in a dissociated state, preventing it from inhibiting cGMP PDE6, thereby allowing the enzyme to catalyze the conversion of cGMP into GMP.[15] A review by Cote et al. (2021) highlights that the binding of two Tα subunits to PDEγ causes a conformational shift exposing the PDE6 active-site.[16]

In a dark state (inactive) rod cell, there is a steady influx of cations through cGMP-gated Na^+/Ca^{2+} channels. Thus, the rod cell maintains a depolarized state, resulting in steady synaptic release of the neurotransmitter glutamate. The hydrolysis of cGMP into GMP rapidly reduces cGMP levels, shifting the ligand-binding equilibrium of cGMP-gated Na^+/Ca^{2+} channels on the rod outer segment and causing the closure of these channels.[4] This halts ion influx and rapid rod cell hyperpolarization. Subsequently, glutamate release at synapses decreases or stops completely, modifying bipolar cell signaling and impacting ganglion cell activity. This change in electrical signaling propagates through the optic nerve, ultimately resulting in visual perception.[4]

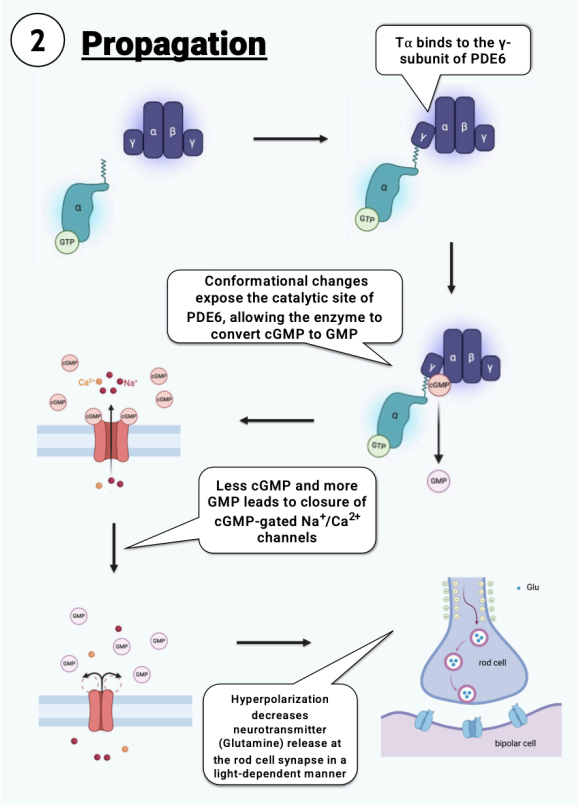

Figure 10. A schematic highlighting the steps involved in signal propagation.

VI. Signal Termination

The termination of phototransduction signaling involves two main steps: hydrolyzing the γ-phosphate on Tα bound GTP and decoupling transducin from rhodopsin. Because transducin has low intrinsic GTPase activity, deactivation of Tα is catalyzed by the GTPase-accelerating protein (GAP) complex R9AP-RGS9-1-Gβ5L. In the GAP complex, RGS9-1 facilitates the hydrolysis of the γ-phosphate on Tα bound GTP. Following hydrolysis, GDP bound Tα is inactive and spontaneously dissociates from PDEγ, which then reasserts its inhibition on PDE6 **(Figure 11).**[4]

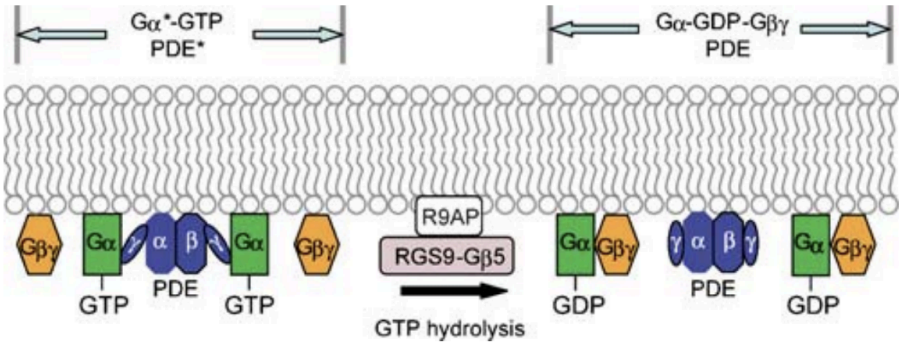

Figure 11. A schematic showing the termination of PDE6 inhibition by Tα (Gα).[4\]

The termination of signaling on the GPCR rhodopsin begins with phosphorylation of activated rhodopsin by rhodopsin kinase 1 (GRK1). This step reduces rhodopsin's affinity for transducin and primes it for arrestin binding. Sokal et al. (2002) demonstrated that GRK1 selectively phosphorylates serine and threonine residues on the C-terminal cytoplasmic tail of Metarhodopsin II, introducing negative charges which decrease transducin binding affinity by ~50%.[17] This phosphorylation event is facilitated by the

conformational rearrangements following retinal isomerization, which expose GRK1 phosphorylation sites that remain inaccessible in the inactive state. Moreover, GRK1 activity is dynamically regulated by the calcium-binding protein recoverin, which sterically hinders GRK1 under dark conditions when intracellular Ca^{2+} levels are high. As phototransduction proceeds and Ca^{2+} levels drop, recoverin is freed, positioning GRK1 to adopt a favorable conformation for phosphorylation of rhodopsin.[18]

Once phosphorylated, rhodopsin rapidly binds arrestin, which sterically blocks further transducin coupling. Structural insights into the mechanism of arrestin binding show that arrestin undergoes a large-scale conformational change upon interaction with phosphorylated rhodopsin.[19, 20] Specifically, one contact site on rhodopsin can interact with multiple residues on arrestin that are more than 30 Å apart, suggesting that arrestin takes on conformational changes which lead to rhodopsin deactivation.[21] Arrestin's N-terminal domain has been found to interact with phosphorylated residues on rhodopsin, while its C-terminal domain undergoes a rotation that locks rhodopsin into an inactive conformation.[20,21]

Beyond simply blocking transducin binding, arrestin facilitates receptor internalization by linking rhodopsin to the clathrin-mediated endocytic pathway. Arrestin contains clathrin-binding motifs, allowing it to recruit adaptor protein 2 (AP-2) and clathrin, targeting phosphorylated rhodopsin for vesicular trafficking. This ensures long-term signal termination and prevents rhodopsin from aberrantly re-entering the phototransduction cascade. Arrestin-bound rhodopsin can either be dephosphorylated and recycled back to the outer segment or subject to lysosomal degradation depending on the physiological conditions and the receptor's light exposure history.[22]

VII. Retinal Restoration

Following arrestin-mediated inactivation, rhodopsin must be regenerated to its inactive state. The all-*trans*-retinal chromophore remains covalently linked to rhodopsin. It must be released and enzymatically be converted back to 11-*cis*-retinal and then reloaded into rhodopsin. This occurs via a multistep enzymatic pathway that predominantly takes place in the retinal pigment epithelium (RPE).[4] Retinal dehydrogenases (RDH8 and RDH12) first reduce all-*trans*-retinal to all-*trans*-retinol, which is then transported to the RPE. Within the RPE, lecithin retinol acyltransferase (LRAT) and retinal epithelium-specific 65 kDa protein (RPE65) catalyze the reconversion of all-*trans*-retinol to 11-*cis*-retinal (**Figure 10**). The regenerated 11-*cis*-retinal is shuttled back to the photoreceptor outer segment, where it binds to rhodopsin and restores it to its light-sensitive state.

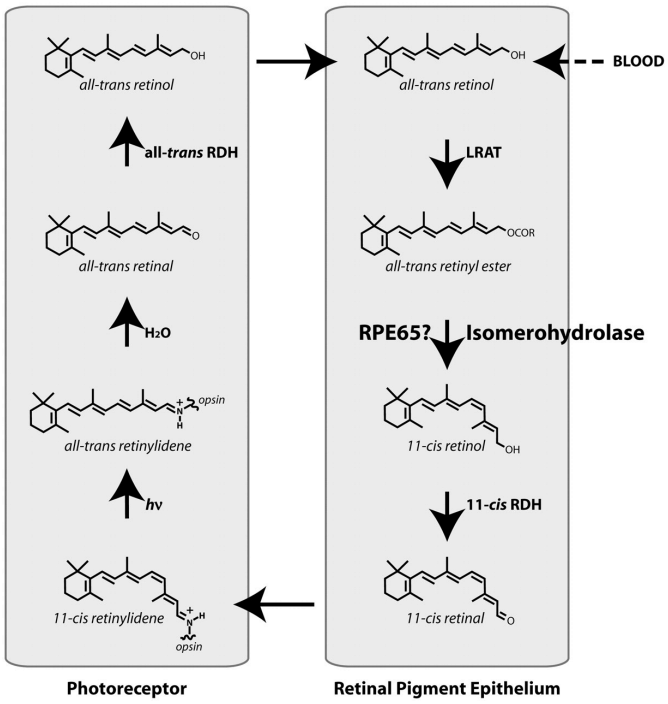

Figure 10. A schematic of the enzymatic pathway for the recycling of 11-*cis*-retinal (retinoid visual cycle).[23]

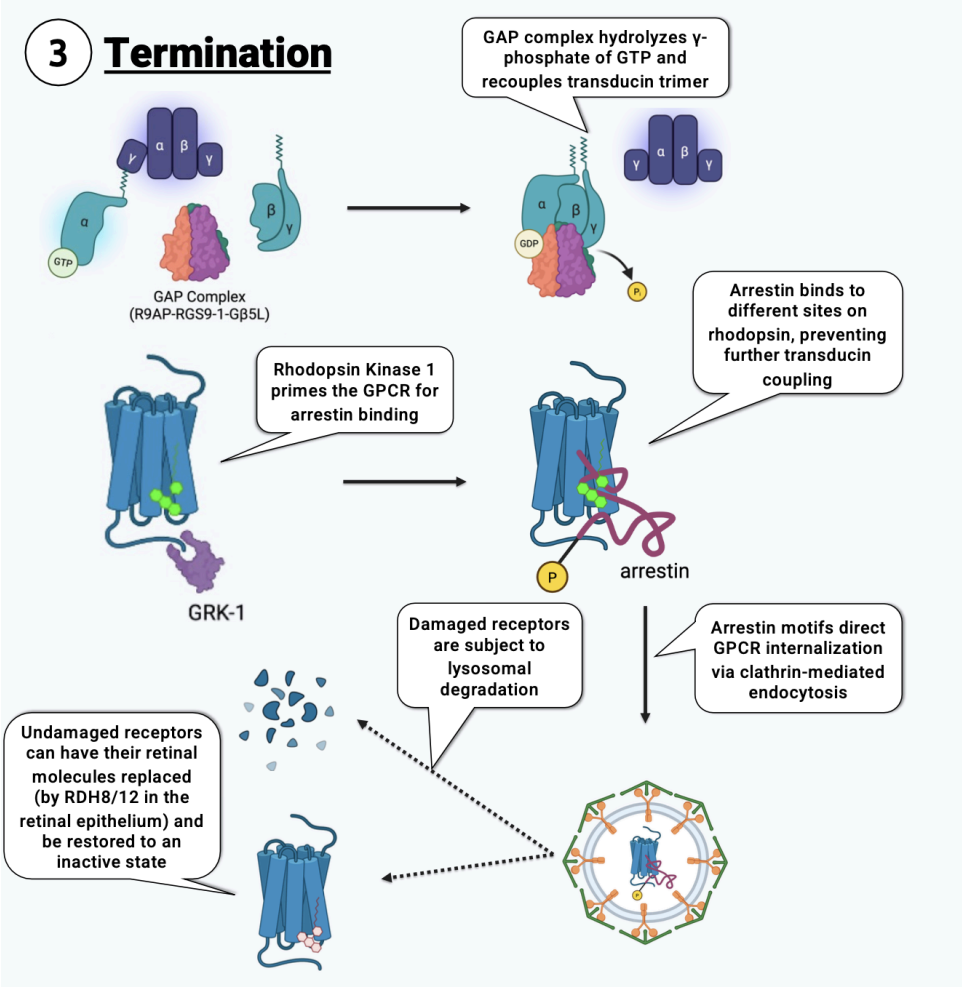

Figure 11. A simplified schematic highlighting the key steps in the termination stage of phototransduction.

VIII. Conclusion

Phototransduction is a tightly regulated cascade that begins with the photoisomerization of 11-*cis*-retinal and ends with visual perception. At the heart of the process is rhodopsin, a GPCR that transduces light into intracellular signals via G-protein (transducin) activation. Structural and biochemical studies have elucidated how ligand-induced changes–particularly deprotonation of the Schiff base and outward movement of TM6–drive rhodopsin into its active conformation, exposing a cytoplasmic crevice for transducin binding. Once activated, transducin interacts with the second

messenger enzyme PDE6 to amplify the photosignal.

Signal resolution involves phosphorylation by GRK1 followed by arrestin-binding and then chromophore recycling. While recent advances in crystallography, cryo-EM, and spectroscopy have mapped much of the rhodopsin activation cycle, mechanistic gaps remain–especially concerning transducin's dynamic association and dissociation. Continued integration of high-resolution techniques and computational modeling will be critical for understanding these remaining aspects, with implications not only for vision but for GPCR signaling as a whole.

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