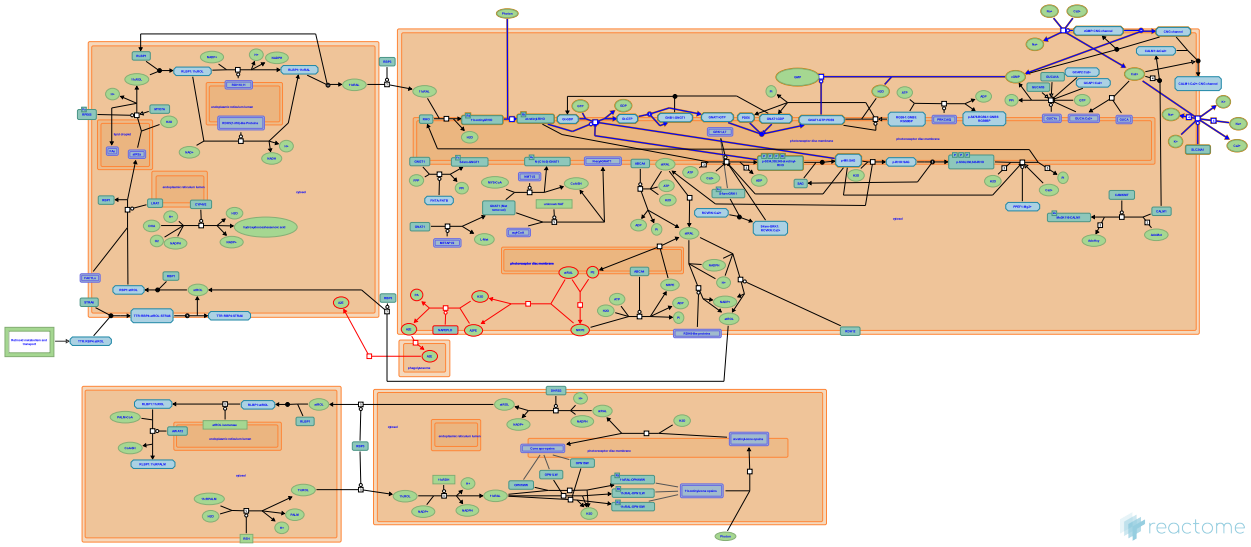
Activation of the phototransduction cascade



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18/05/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

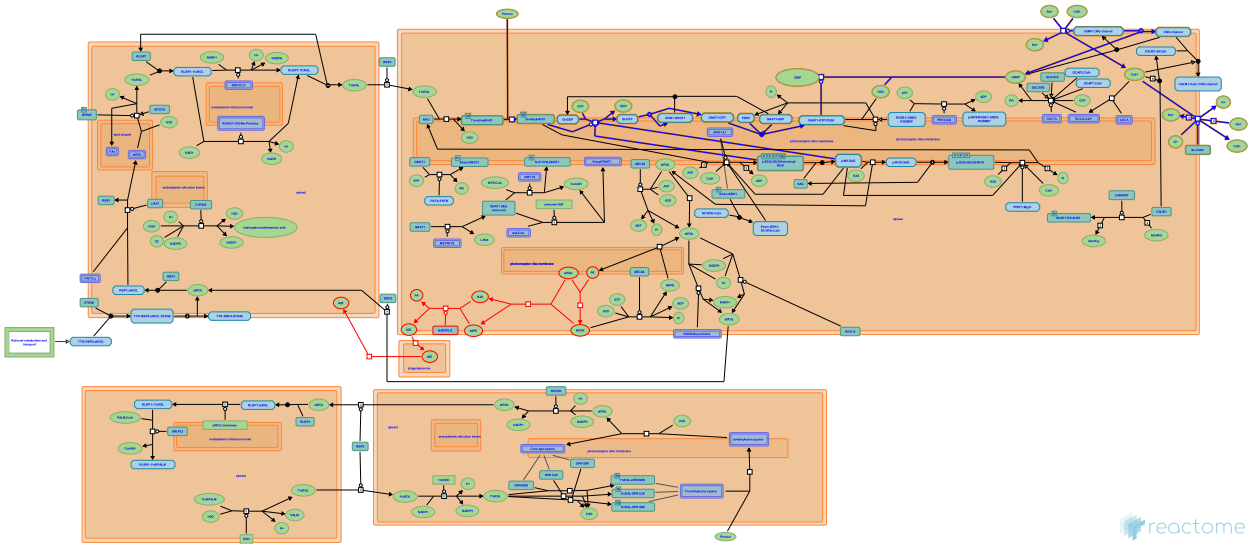
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Activation of the phototransduction cascade ↗

Stable identifier: R-HSA-2485179



The photoreceptor cascade starts with light isomerization of 11-cis-retinal (11cRAL) of rhodopsin (RHO) to all-trans-retinal (atRAL), inducing a conformational change in RHO to the active, metarhodopsin II (MII) state. MII activates the G protein transducin (Gt) that in turn activates phosphodiesterase 6 (PDE6). Consequently, there is a fall in the intracellular concentration of cGMP that closes cGMP-dependent cation channels (CNG channels) and hyperpolarizes the rod. This has the effect of reducing or stopping glutamate release from synaptic vesicles thus signalling to the surrounding cells how many photons were absorbed (Burns & Pugh 2010, Korenbrot 2012, Pugh & Lamb 1993).

Literature references

Pugh, EN., Lamb, TD. (1993). Amplification and kinetics of the activation steps in phototransduction. *Biochim. Biophys. Acta, 1141*, 111-49. ↗

Korenbrot, JI. (2012). Speed, sensitivity, and stability of the light response in rod and cone photoreceptors: facts and models. *Prog Retin Eye Res, 31*, 442-66. ↗

Pugh, EN., Burns, ME. (2010). Lessons from photoreceptors: turning off G-protein signaling in living cells. *Physiology (Bethesda), 25*, 72-84. ↗

Editions

2012-10-01	Authored, Edited	Jassal, B.
2013-04-11	Reviewed	Makino, C.

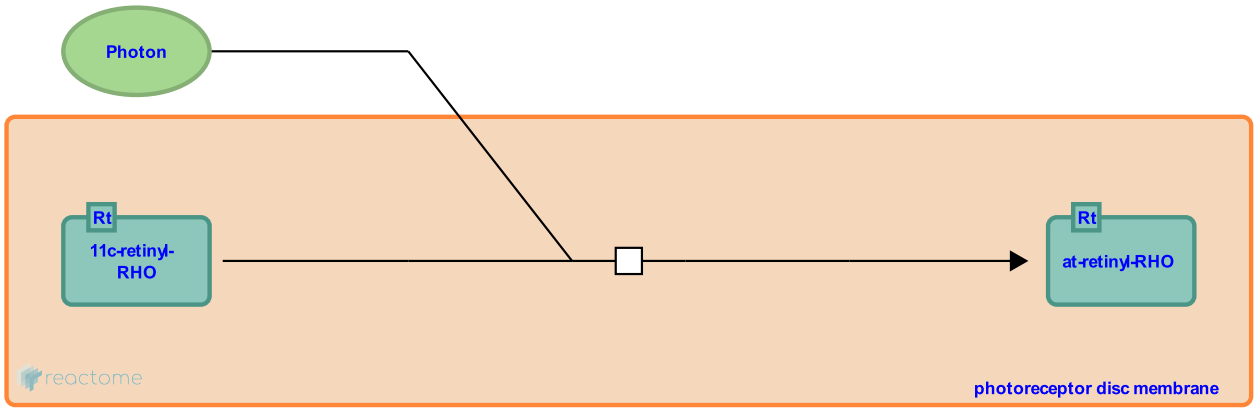
Photons induce isomerization of 11c-retinyl to at-retinyl ↗

Location: Activation of the phototransduction cascade

Stable identifier: R-HSA-74101

Type: transition

Compartments: photoreceptor disc membrane, extracellular region



The visual pigment rhodopsin consists of a seven transmembrane helix protein, opsin (RHO), to which an 11-cis-retinal (11cRAL) chromophore is bound as a protonated Schiff base (Hargrave et al. 1983, Nathans & Hogness 1984, Ovchinnikov et al. 1983). The covalent bond between opsin and its 11-cis-retinyl (11c-retinyl) ligand, which is unique among G protein coupled receptors, helps to confer extraordinary stability in darkness (Baylor et al. 1984). 11cRAL is an inverse agonist, that quenches the weak ability of opsin to activate transducin G protein (Gt). Upon photon absorption, the bound 11c-retinyl group isomerizes in a few hundred femtoseconds (Schoenlein et al. 1991) and with a high quantum efficiency of 0.7 (Dartnall 1968) to the bound all-trans-retinyl (at-retinyl) isomer. Then in the next few milliseconds, opsin undergoes a rearrangement in structure that renders it catalytically active (MII aka metarhodopsin II or R*) (Emeis et al. 1982). The isomerisation is a very fast photochemical process (femtoseconds) followed by slower events (Smith 2010).

Mutations in RHO can give rise to autosomal dominant or recessive forms of retinitis pigmentosa or autosomal dominant congenital stationary night blindness (https://sph.uth.edu/retnet/). Retinitis pigmentosa is a progressive form of blindness marked by an initial degeneration of rods, followed by the secondary loss of cones.

Followed by: MII catalyses GDP/GTP exchange on Gt

Literature references

Fe□gina, MIu., Ovchinnikov, IuA., Artamonov, ID., Abdulaev, NG., Bogachuk, AS. (1983). [Visual rhodopsin. III. Complete amino acid sequence and topography in a membrane]. *Bioorg. Khim., 9*, 1331-40. ↗

Smith, SO. (2010). Structure and activation of the visual pigment rhodopsin. *Annu Rev Biophys, 39*, 309-28. ↗

Wang, JK., Rao, JK., Argos, P., McDowell, JH., Juszczak, E., Curtis, DR. et al. (1983). The structure of bovine rhodopsin. *Biophys. Struct. Mech., 9*, 235-44. ↗

Reichert, J., Kühn, H., Emeis, D., Hofmann, KP. (1982). Complex formation between metarhodopsin II and GTP-binding protein in bovine photoreceptor membranes leads to a shift of the photoproduct equilibrium. *FEBS Lett., 143*, 29-34. ↗

Nunn, BJ., Schnapf, JL., Baylor, DA. (1984). The photocurrent, noise and spectral sensitivity of rods of the monkey Macaca fascicularis. *J. Physiol. (Lond.), 357*, 575-607. ↗

Editions

2003-07-11	Authored	Schmidt, EE.
2012-08-21	Authored, Edited	Jassal, B.
2013-01-31	Reviewed	Blaner, WS.

MII catalyses GDP/GTP exchange on Gt ↗

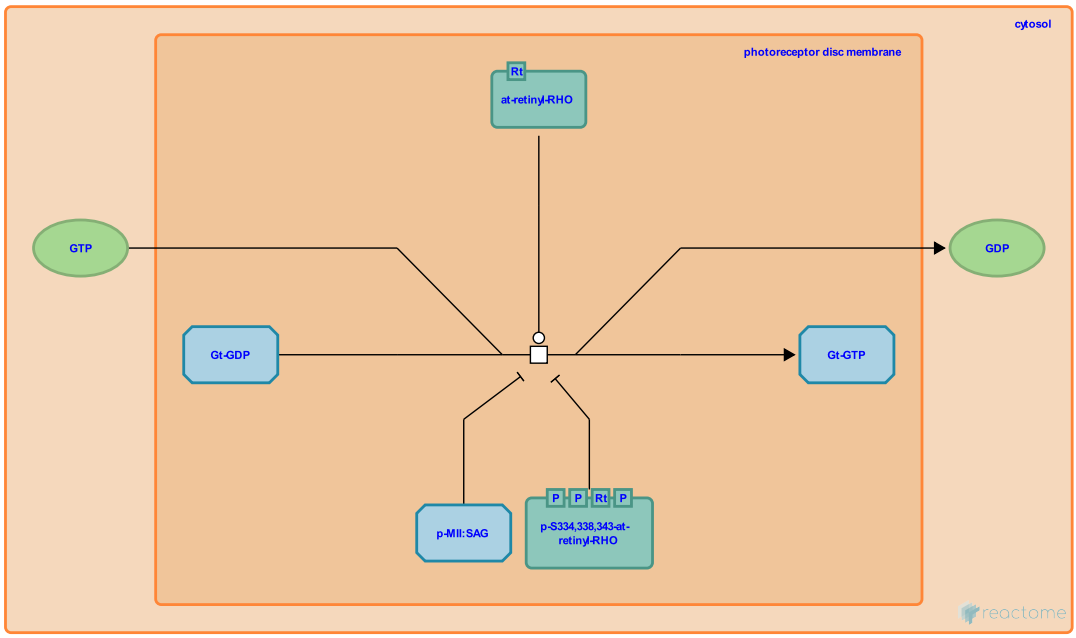
Location: Activation of the phototransduction cascade

Stable identifier: R-HSA-2485180

Type: transition

Compartments: photoreceptor disc membrane, cytosol

Inferred from: MII catalyses GDP/GTP exchange on Gt (Bos taurus)



In darkness, the G protein transducin (Gt) is attached to the disk membrane surface with a GDP bound to it and it is inactive. Gt is a heterotrimer of alpha1 (GNAT1) (van Dop et al. 1989, Fong 1992), beta1 (GNB1) (Codina et al. 1986) and gamma1 (GNGT1) (Tao et al. 1993) subunits. Photoactivated rhodopsin (MII or R*) catalyzes the exchange of GTP for GDP bound to Gt. Upon GTP/GDP exchange, Gt is released from MII and the Gt alpha with GTP bound (GNAT1 GTP) dissociates from Gt beta gamma subunits (GNB1:GNGT1). This mechanism was deciphered from bovine experiments (Pugh & Lamb 1993). MII proceeds to activate additional Gt molecules, making this reaction the first amplification step in the phototransduction cascade. A single activated rhodopsin molecule activates tens of Gt molecules. Although phosphorylation of activated rhodopsin (MII) by rhodopsin kinase (GRK1) reduces transducin activation (Khani et al. 1996), complete deactivation occurs only after arrestin (S-antigen or SAG, Yamaki et al. 1988) binds to and sterically caps MII.

Defects in GNAT1 cause the Nougaret type of autosomal dominant, congenital stationary night blindness (Dryja et al. 1996, CSNBAD3; MIM:610444) . Congenital stationary night blindness is a non progressive retinal disorder characterized by impaired night vision.

Preceded by: Photons induce isomerization of 11c-retinyl to at-retinyl

Followed by: Gt-GTP dissociates to GNAT1-GTP and GNB1:GNGT1

Literature references

Fong, SL. (1992). Characterization of the human rod transducin alpha-subunit gene. *Nucleic Acids Res., 20*, 2865-70. ↗

Pugh, EN., Lamb, TD. (1993). Amplification and kinetics of the activation steps in phototransduction. *Biochim. Biophys. Acta, 1141*, 111-49. ↗

Hahn, LB., Reboul, T., Arnaud, B., Dryja, TP. (1996). Missense mutation in the gene encoding the alpha subunit of rod transducin in the Nougaret form of congenital stationary night blindness. *Nat Genet, 13*, 358-60. ↗

Stengel, D., Birnbaumer, L., Woo, SL., Codina, J. (1986). Beta-subunits of the human liver Gs/Gi signal-transducing proteins and those of bovine retinal rod cell transducin are identical. *FEBS Lett, 207*, 187-92. ↗

Van Dop, C., Apone, LM., Medynski, DC. (1989). Nucleotide sequence for a cDNA encoding the alpha subunit of retinal transducin (GNAT1) isolated from the human eye. *Nucleic Acids Res, 17*, 4887. ↗

Editions

2012-10-01	Authored, Edited	Jassal, B.
2013-04-11	Reviewed	Makino, C.

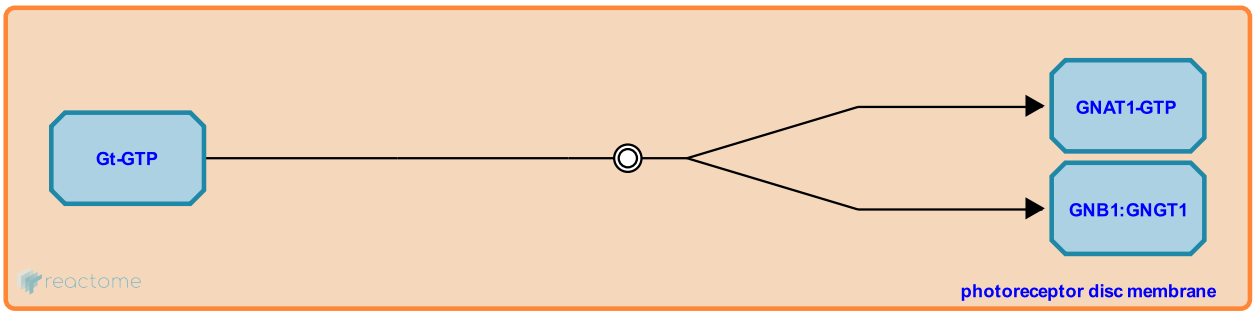
Gt-GTP dissociates to GNAT1-GTP and GNB1:GNGT1 ↗

Location: Activation of the phototransduction cascade

Stable identifier: R-HSA-2485182

Type: dissociation

Compartments: photoreceptor disc membrane



Binding of transducin (Gt) to activated rhodopsin (MII) promotes the release of GDP from the Gt alpha subunit enabling a GTP (present in a higher concentration than GDP) to take its place. With GTP bound, Gt alpha (GNAT1-GTP) dissociates from the Gt beta:gamma subunits (GNB1:GNGT1) and from MII. MII is then available to bind and activate additional transducins. Transducin activation is the first amplifying step in visual transduction. Many findings came from bovine experiments (Pugh & Lamb 1993, Fung & Stryer 1980, Fung et al. 1981, Hofmann 1985).

Preceded by: MII catalyses GDP/GTP exchange on Gt

Followed by: GNAT1-GTP binds PDE6 and activates it

Literature references

Pugh, EN., Lamb, TD. (1993). Amplification and kinetics of the activation steps in phototransduction. *Biochim. Biophys. Acta, 1141*, 111-49. ↗

Fung, BK., Hurley, JB., Stryer, L. (1981). Flow of information in the light-triggered cyclic nucleotide cascade of vision . *Proc. Natl. Acad. Sci. U.S.A., 78*, 152-6. ↗

Hofmann, KP. (1985). Effect of GTP on the rhodopsin-G-protein complex by transient formation of extra metarhodopsin II. *Biochim. Biophys. Acta, 810*, 278-81. ↗

Kwok-Keung Fung, B., Stryer, L. (1980). Photolyzed rhodopsin catalyzes the exchange of GTP for bound GDP in retinal rod outer segments. *Proc. Natl. Acad. Sci. U.S.A., 77*, 2500-4. ↗

Editions

2012-10-01	Authored, Edited	Jassal, B.
2013-04-11	Reviewed	Makino, C.

GNAT1-GTP binds PDE6 and activates it ↗

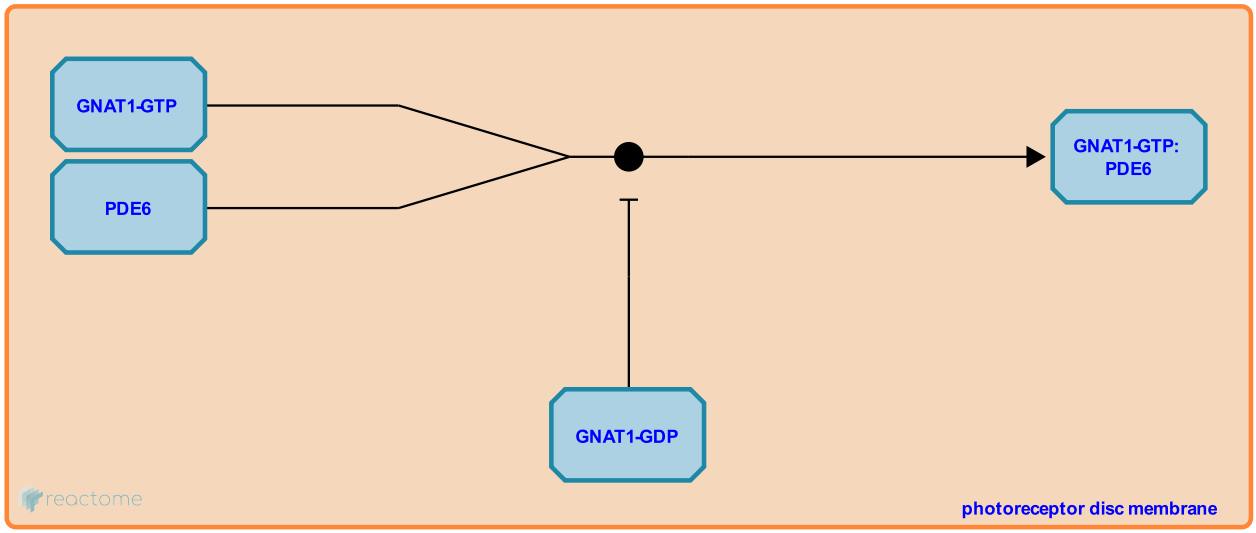
Location: Activation of the phototransduction cascade

Stable identifier: R-HSA-74065

Type: binding

Compartments: photoreceptor disc membrane, cytosol

Inferred from: Gnat1-GTP binds Pde6 and activates it (Bos taurus)



The membrane associated cGMP phosphodiesterase 6 (PDE6) is a tetramer of two catalytic chains, alpha (PDE6A or PDEA) (Pittler et al. 1990) and beta (PDE6B or PDEB) (Weber et al. 1991), and two inhibitory gamma chains (PDE6G or PDEG) (Tuteja et al. 1990). Binding of an activated transducin alpha subunit (GNAT1-GTP) to PDE-gamma relaxes the inhibitory effect of the gamma subunit thereby activating the associated alpha or beta catalytic subunit. Because the binding of GNAT1-GTP to PDE-gamma is one to one, there is no amplification associated with this step. Active Gt alpha (GNAT-GTP) can be inactivated by a slow, intrinsic GTPase activity that hydrolyses GTP to GDP. Once GNAT1 has GDP bound, it no longer binds to the gamma subunit of PDE6 (PDE6-gamma) that then resumes inhibition of the catalytic subunit of PDE6. Some forms of autosomal recessive retinitis pigmentosa and congenital stationary night blindness are caused by mutations in PDE6 (https://sph.uth.edu/retnet/).

Preceded by: Gt-GTP dissociates to GNAT1-GTP and GNB1:GNGT1

Followed by: PDE6 hydrolyses cGMP to GMP

Literature references

Mohandas, T., Sparkes, RS., Tuteja, R., Inana, G., Danciger, M., Klisak, I. et al. (1990). Isolation and characterization of cDNA encoding the gamma-subunit of cGMP phosphodiesterase in human retina. *Gene, 88*, 227-32. ↗

Ledbetter, D., Davis, RL., Champagne, MS., vanTuinen, P., Wasmuth, JJ., McConnell, DG. et al. (1990). Molecular characterization of human and bovine rod photoreceptor cGMP phosphodiesterase alpha-subunit and chromosomal localization of the human gene. *Genomics, 6*, 272-83. ↗

Lin, BY., Riess, O., Weber, B., Hutchinson, G., Kowbel, D., Schappert, K. et al. (1991). Genomic organization and complete sequence of the human gene encoding the beta-subunit of the cGMP phosphodiesterase and its localisation to 4p 16.3. *Nucleic Acids Res., 19*, 6263-8. ↗

Editions

2003-07-11	Authored	Schmidt, EE.
2012-09-18	Edited	Jassal, B.
2013-04-11	Reviewed	Makino, C.

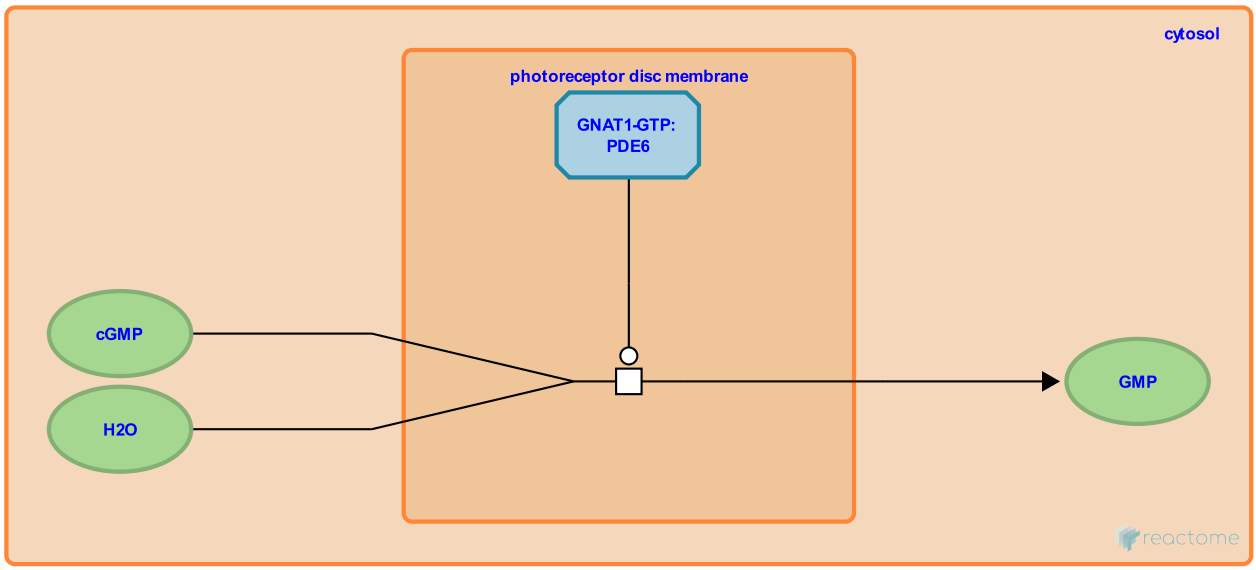
PDE6 hydrolyses cGMP to GMP ↗

Location: Activation of the phototransduction cascade

Stable identifier: R-HSA-74059

Type: transition

Compartments: photoreceptor disc membrane, cytosol



Phosphodiesterase 6 (PDE6, Pittler et al. 1990, Tuteja et al. 1990, Weber et al. 1991) undergoes brief, spontaneous activations every few minutes to sustain a low, basal rate of 3',5' cyclic GMP (cGMP) hydrolysis to 5' GMP (Cobbs 1991, Dawis et al. 1988, Hodgkin & Nunn 1988, Rieke & Baylor 1996, Wensel & Stryer 1986). However, activated transducin (GNAT1-GTP) sustains PDE6 activation allowing it to hydrolyze cGMP at a rate limited only by diffusional access to substrate (Chader et al. 1974, Goridis & Virmaux 1974, Miki et al. 1973). This event represents another amplification step in the phototransduction cascade wherein activated PDE6 hydrolyzes thousands of cGMP molecules per second. The decline in intracellular cGMP levels results in the closure of cyclic nucleotide gated cation channels (CNG channels). Mutations in the PDE6 subunits can cause retinitis pigmentosa or congenital stationary night blindness (https://sph.uth.edu/retnet/).

Preceded by: GNAT1-GTP binds PDE6 and activates it

Followed by: cGMP dissociates from CNG channels

Literature references

Hodgkin, AL., Nunn, BJ. (1988). Control of light-sensitive current in salamander rods. *J. Physiol. (Lond.), 403*, 439-71. ↗

Dawis, SM., Walseth, TF., Heyman, RA., Graeff, RM., Goldberg, ND. (1988). Regulation of cyclic GMP metabolism in toad photoreceptors. Definition of the metabolic events subserving photoexcited and attenuated states. *J. Biol. Chem., 263*, 8771-85. ↗

Cobbs, WH. (1991). Light and dark active phosphodiesterase regulation in salamander rods. *J. Gen. Physiol., 98*, 575-614. ↗

Mohandas, T., Sparkes, RS., Tuteja, R., Inana, G., Danciger, M., Klisak, I. et al. (1990). Isolation and characterization of cDNA encoding the gamma-subunit of cGMP phosphodiesterase in human retina. *Gene, 88*, 227-32. ↗

Rieke, F., Baylor, DA. (1996). Molecular origin of continuous dark noise in rod photoreceptors. *Biophys. J., 71*, 2553-72. ↗

Editions

2003-07-11	Authored	Schmidt, EE.
2012-10-24	Edited	Jassal, B.
2013-04-11	Reviewed	Makino, C.

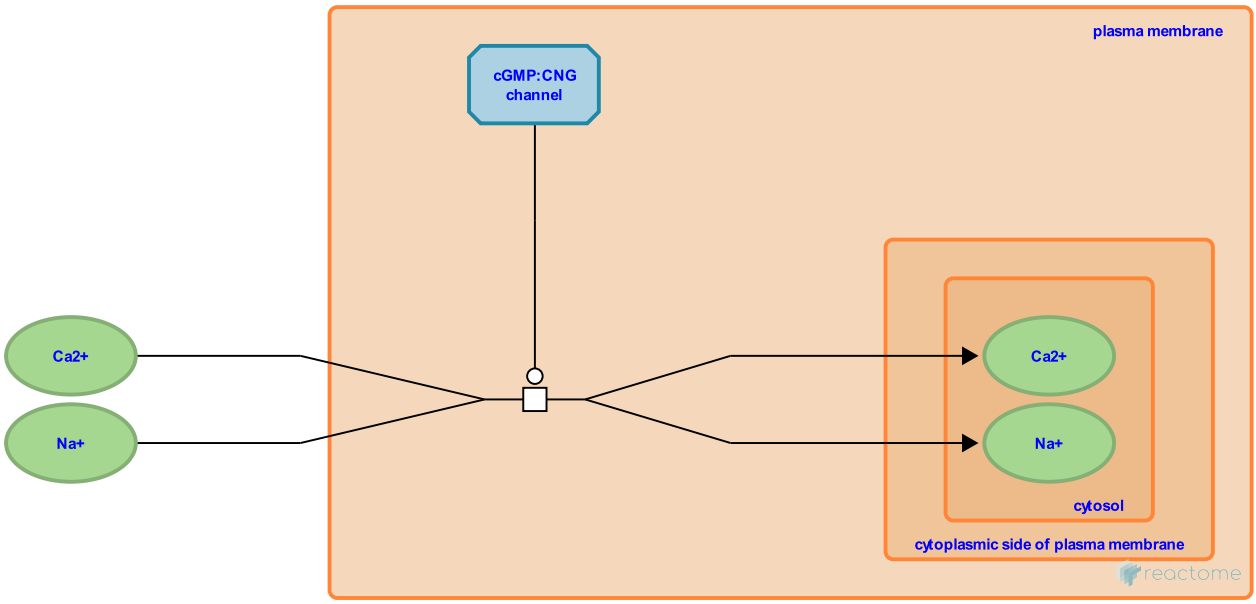
cGMP:CNG transports Na+ and Ca2+ into the rod outer segment ↗

Location: Activation of the phototransduction cascade

Stable identifier: R-HSA-2514867

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



The cGMP-gated (CNG) channels are heterotetramers of three alpha subunits (CNGA1) and one beta subunit (CNGB1). Although the subunits bear structural similarities to voltage-gated potassium channels, the rod channel is only weakly voltage sensitive (Chen et al. 1993). Opening occurs with cGMP bound and rarely occurs in the absence of cGMP (hence the closed state is designated as CNG channel and the open status is designated as cGMP:CNG channel). In darkness, cGMP concentration is relatively high and cGMP-gated cation (CNG) channels are open to allow the influx of cations into the rod outer segment. The inward current is composed mainly of Na+ ions, with lesser contributions from Ca2+ ions and Mg2+ ions (Dhallan et al. 1992). The channel is outwardly rectifying so that over physiological membrane potentials, the inward current is proportional to the number of channels open and is nearly independent of voltage. Mutations in the CNG channel subunits can cause a recessive form of retinitis pigmentosa (https://sph.uth.edu/retnet/).

Followed by: SLC24A1 exchanges 4Na+ for Ca2+, K+

Literature references

Yau, KW., Zhong, H., Molday, LL., Molday, RS. (2002). The heteromeric cyclic nucleotide-gated channel adopts a 3A:1B stoichiometry. *Nature, 420*, 193-8. ↗

Zagotta, WN., Craven, KB. (2006). CNG and HCN channels: two peas, one pod. *Annu. Rev. Physiol., 68*, 375-401. ↗

Ficek, N., Bauer, PJ., Weitz, D., Kremmer, E., Kaupp, UB. (2002). Subunit stoichiometry of the CNG channel of rod photoreceptors. *Neuron, 36*, 881-9. ↗

Reed, RR., Yau, KW., Nathans, J., Macke, JP., Dhallan, RS., Shows, TB. (1992). Human rod photoreceptor cGMP-gated channel: amino acid sequence, gene structure, and functional expression. *J Neurosci, 12*, 3248-56. ↗

Zheng, J., Zagotta, WN., Trudeau, MC. (2002). Rod cyclic nucleotide-gated channels have a stoichiometry of three CNGA1 subunits and one CNGB1 subunit. *Neuron, 36*, 891-6. ↗

Editions

2012-10-11	Authored, Edited	Jassal, B.
2013-04-11	Reviewed	Makino, C.

SLC24A1 exchanges 4Na+ for Ca2+, K+ ↗

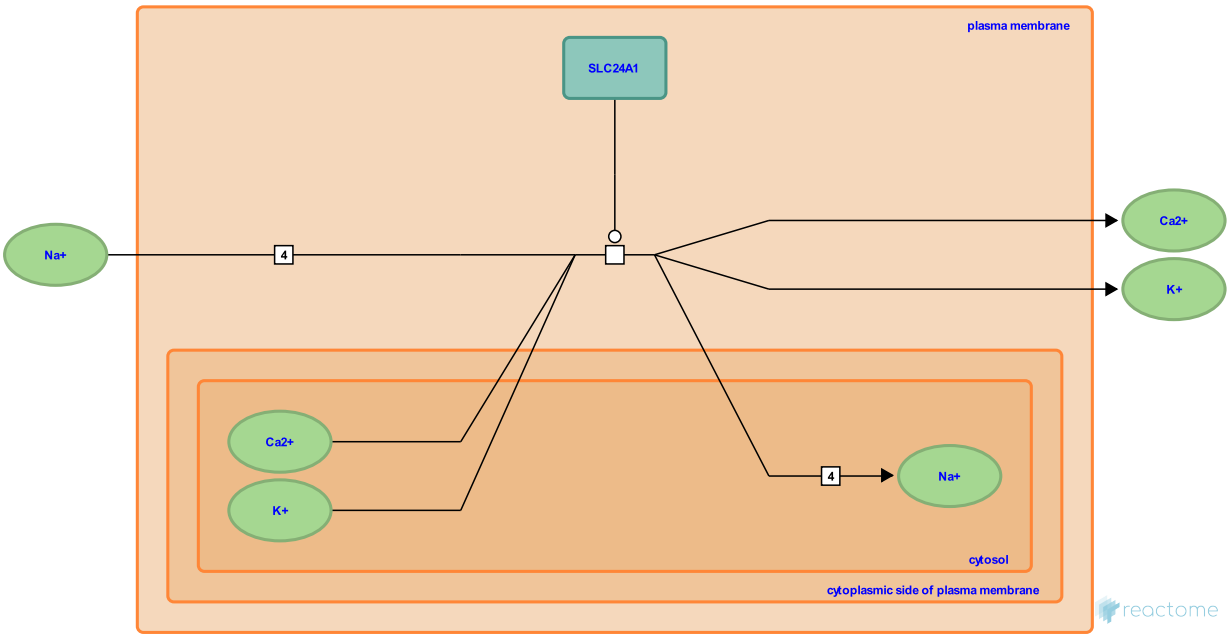
Location: Activation of the phototransduction cascade

Stable identifier: R-HSA-2514891

Type: transition

Compartments: plasma membrane, extracellular region, cytosol

Inferred from: Nckx1 exchanges Na+ for Ca2+/K+ (Bos taurus)



Intracellular Ca2+ is extruded from the outer segment by a Na+/Ca2+, K+ exchanger (NCKX1 encoded by SLC24A1) (Tucker et al. 1998). Operation of the exchanger is electrogenic; 4 Na+ enter and 1 K+ exits for every Ca2+ removed for a net movement of 1 positive charge inward per duty cycle. In bright light, when all of the CNG channels are closed, the exchanger continues to remove Ca2+, reducing intracellular Ca2+ by an order of magnitude. Mutations in SLC24A1 can give rise to recessive congenital stationary night blindness (Riazuddin et al. 2010).

Preceded by: cGMP:CNG transports Na+ and Ca2+ into the rod outer segment

Literature references

Tucker, JE., Schnetkamp, PP., Winkfein, RJ., Cooper, CB. (1998). cDNA cloning of the human retinal rod Na-Ca + K exchanger: comparison with a revised bovine sequence. *Invest Ophthalmol Vis Sci, 39*, 435-40. ↗

Hejtmancik, JF., Khan, SN., Ponferrada, VG., Husnain, T., Riazuddin, SA., Audo, I. et al. (2010). A mutation in SLC24A1 implicated in autosomal-recessive congenital stationary night blindness. *Am. J. Hum. Genet., 87*, 523-31. ↗

Editions

2012-10-11	Authored, Edited	Jassal, B.
2013-04-11	Reviewed	Makino, C.

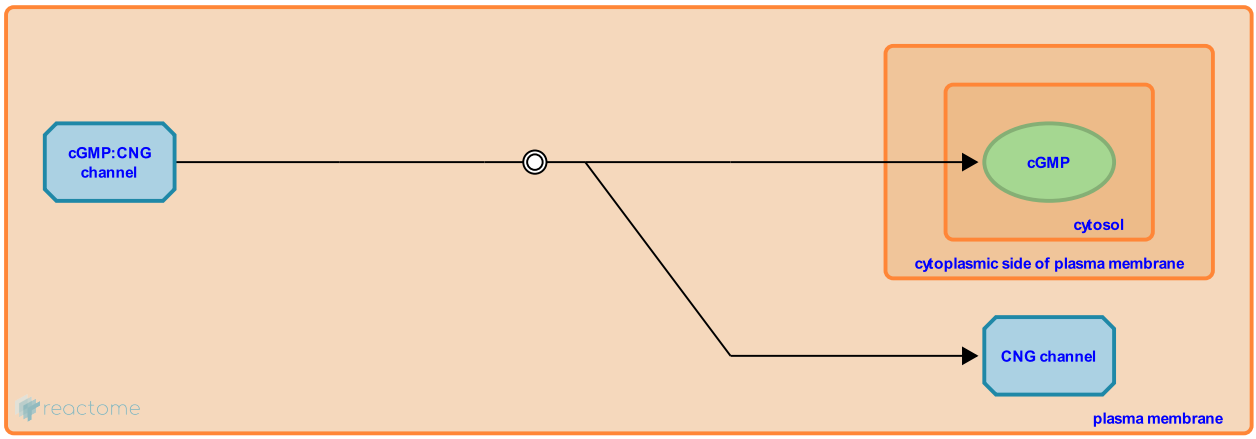
cGMP dissociates from CNG channels ↗

Location: Activation of the phototransduction cascade

Stable identifier: R-HSA-2514865

Type: dissociation

Compartments: plasma membrane, cytosol



As cGMP is hydrolysed during the activation phase of phototransduction, its intracellular concentration decreases leading to the closure of CNG channel (the closed status is designated as CNG channel) (Dhallan et al. 1992, Chen et al. 1993). Channel closure reduces the inward flux of sodium and calcium (also known as the 'dark current') resulting in cell hyperpolarisation. Cooperative binding of cGMP to the CNG channel confers additional amplification to the phototransduction cascade (Pugh & Lamb 1993, Yau & Baylor 1989).

Preceded by: PDE6 hydrolyses cGMP to GMP

Literature references

Pugh, EN., Lamb, TD. (1993). Amplification and kinetics of the activation steps in phototransduction. *Biochim. Biophys. Acta, 1141*, 111-49. ↗

Yau, KW., Baylor, DA. (1989). Cyclic GMP-activated conductance of retinal photoreceptor cells. *Annu. Rev. Neurosci., 12*, 289-327. ↗

Reed, RR., Yau, KW., Nathans, J., Macke, JP., Dhallan, RS., Shows, TB. (1992). Human rod photoreceptor cGMP-gated channel: amino acid sequence, gene structure, and functional expression. *J Neurosci, 12*, 3248-56. ↗

Peng, YW., Reed, RR., Yau, KW., Dhallan, RS., Ahamed, B., Chen, TY. (1993). A new subunit of the cyclic nucleotide-gated cation channel in retinal rods. *Nature, 362*, 764-7. ↗

Editions

2012-10-11	Authored, Edited	Jassal, B.
2013-04-11	Reviewed	Makino, C.

Table of Contents