بسم الله الرحمن الرحيم

DOPAMINE SCIENTIFIC TEAM

Visual Transduction

MID | Lecture 1

﴿إِنِّي تَوَكَّلْتُ عَلَى اللَّهِ رَبِّي وَرَبِّكُمْ ۚ مَا مِن دَابَّةٍ إِلَّا هُوَ آخِذٌ بِنَاصِيَتِهَا ۚ إِنَّ رَبِّي عَلَىٰ صِرَاطٍ مُّسْتَقِيمٍ﴾

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Reviewed by: Tala Assaf

BIOCHEMISTRY

رحلة اليقين مع سورة يس

إِنَّا نَحْنُ نُحْيِ ٱلْمَوْتَىٰ وَنَكْتُبُ مَا قَدَّمُوا۟ وَءَاثَـٰرَهُمْ ۚ وَكُلَّ شَىْءٍ أَحْصَيْنَـٰهُ فِىٓ إِمَامٍ مُّبِينٍ (١٢)

{إِنَّا نَحْنُ نُحْيِي الْمَوْتَى } أي: نبعثهم بعد موتهم لنجازيهم على الأعمال، { وَنَكْتُبُ مَا قَدَّمُوا } من الخير والشر، وهو أعمالهم التي عملوها وباشروها في حال حياتهم، { وَآثَارَهُمْ } وهي آثار الخير وآثار الشر، التي كانوا هم السبب في إيجادها في حال حياتهم وبعد وفاتهم، وتلك الأعمال التي نشأت من أقوالهم وأفعالهم وأحوالهم، فكل خير عمل به أحد من الناس، بسبب علم العبد وتعليمه ونصحه، أو أمره بالمعروف، أو نهيه عن المنكر، أو علم أودعه عند المتعلمين، أو في كتب ينتفع بها في حياته وبعد موته، أو عمل خيرا، من صلاة أو زكاة أو صدقة أو إحسان، فاقتدى به غيره، أو عمل مسجدا، أو محلا من المحال التي يرتفق بها الناس، وما أشبه ذلك، فإنها من آثاره التي تكتب له، وكذلك عمل الشر.ولهذا: { من سن سنة حسنة فله أجرها وأجر من عمل بها إلى يوم القيامة، ومن سن سنة سيئة فعليه وزرها ووزر من عمل بها إلى يوم القيامة } وهذا الموضع، يبين لك علو مرتبة الدعوة إلى الله والهداية إلى سبيله بكل وسيلة وطريق موصل إلى ذلك، ونزول درجة الداعي إلى الشر الإمام فيه، وأنه أسفل الخليقة، وأشدهم جرما، وأعظمهم إثما. { وَكُلَّ شَيْءٍ } من الأعمال والنيات وغيرها { أَحْصَيْنَاهُ فِي إِمَامٍ مُبِينٍ } أي: كتاب هو أم الكتب وإليه مرجع الكتب، التي تكون بأيدي الملائكة، وهو اللوح المحفوظ.

Visual transduction

Prof. Mamoun Ahram
Neuroscience, Biochemistry

References

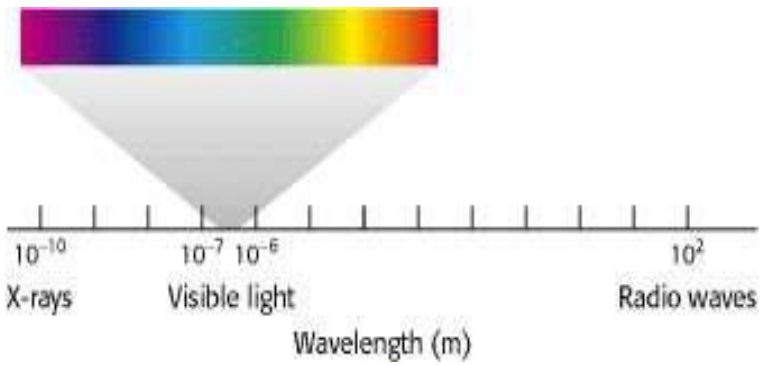
- Webvision: The Organization of the Retina and Visual System (https://www.ncbi.nlm.nih.gov/books/NBK52768/)
- The Molecular Design of Visual Transduction (https://www.biophysics.org/Portals/0/BPSAssets/Articles/Phototransduction.pdf)
- Adaptation of Rod Photoreceptors to Light and Dark (http://photobiology.info/Rozanowska2.html)

Lecture outline

- Visual transduction (dim vs. bright light)
  - Components (cells and molecules)
  - Mechanisms of activation, amplification, and termination
- Color blindness

Basics of human vision

- Light (as a wave) has a huge spectrum of wavelengths, which govern its behavior. Here, for vision, we are only concerned with the wavelengths for the visible light, which is within a narrow range of wavelength (400-700nm).
- For any object, it will reflect specific wavelengths of visible light (our concern) and absorb the rest; our brain interprets the color of that object based on the light rays reflected (the ones that hit our retina). So, a green object is interpreted as green because it reflects light rays of wavelengths that are associated with the color green.



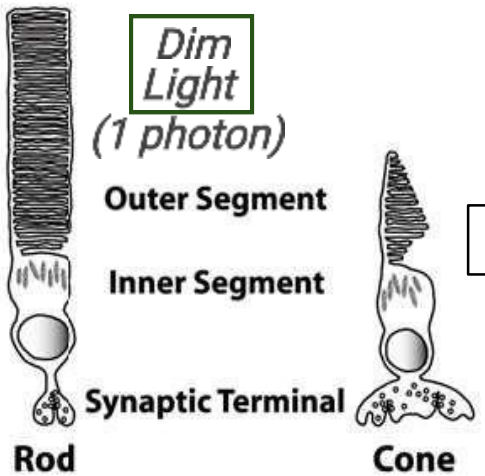
- Colors like blue or violet have smaller wavelengths relative to colors like red and orange, while colors like green and yellow are found at the middle of that spectrum.
  As we said, light isn't limited to what we see. It actually exists within an incredible number of wavelengths that are beyond our visual capabilities. Remember when we talked about spectrophotometry and how DNA absorbs UV waves? DNA interacts mainly with the UV ranges of the spectrum, while it doesn't interact with the visible light, making it transparent.
- Based on our "basic" model of light here: when we are talking about the intensity of the light (its brightness), we're talking about the number of photons. So, a bright light has a huge number of photons; a dim light has a small number of photons.

Rods and cones

أسطوانية مخروطية

What make us see colors 'Cells of vision'
Their names are an indication of their overall shapes
Rods and cones are specialized unipolar neurons

Rods are responsible for vision in dim (dark) light & they can absorb as little as one photon of light indicating a high sensitivity

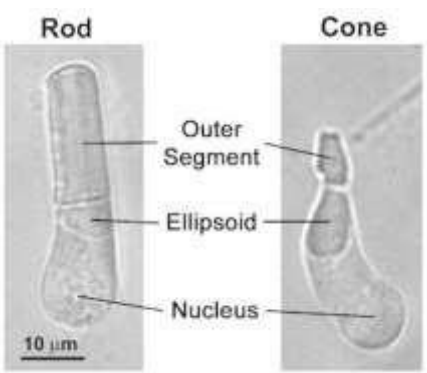


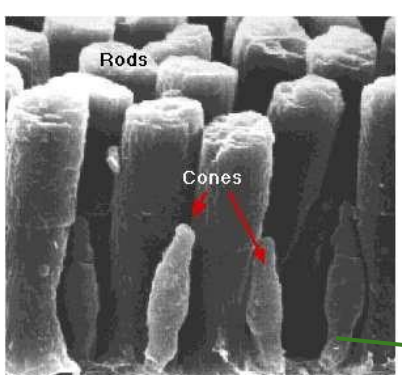
Bright Light

7 million

120 million

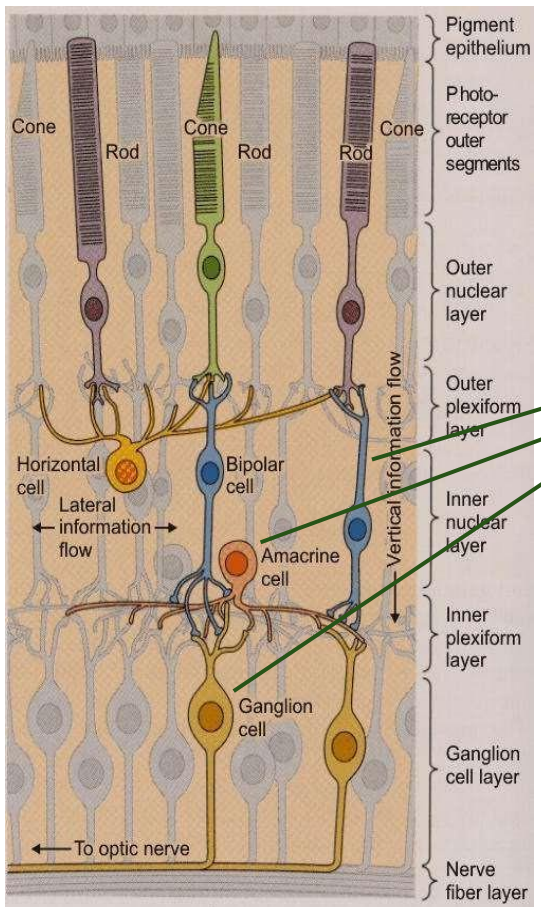
In retina





Picture through SEM

Cones are smaller than rods



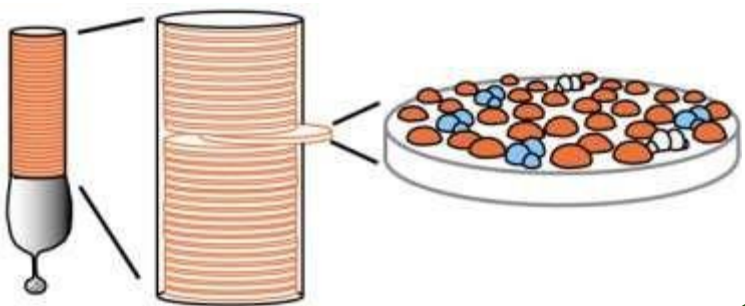
Rods & cones are connected to other types of cells that help them transmit visual signals to the brain

Before we get into the mechanism of transduction know that Cones are found in fewer numbers than rods, which is what makes our understanding of rods far better. (We'll only study the visual transduction through rods, but keep in mind the mechanism is the same for both types of cells.)

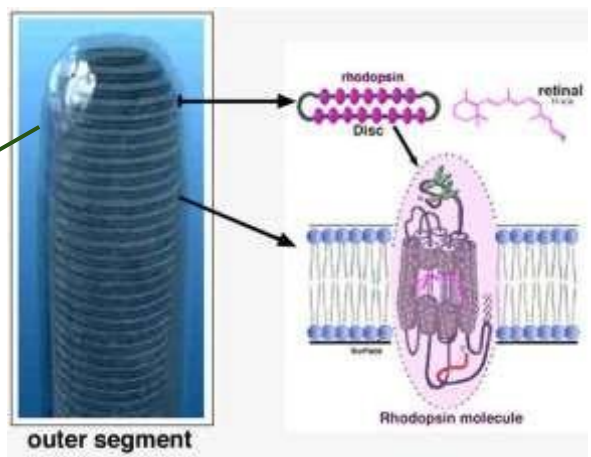
More on rod cells

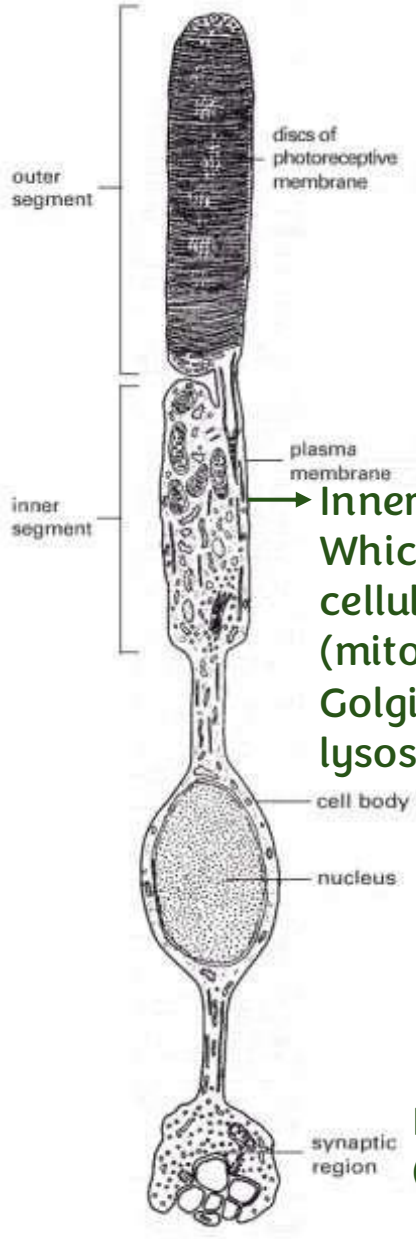
1. Rod cells consist of four regions: The inner segment, the cell body (contains the cellular organelles), and the synaptic region.
2. The outer segment contains the biochemical machinery needed for visual transduction.

The components of the phototransduction enzyme cascade are packed into stacks of membranous vesicles ("disks").



The outer segment is made of discs stacked over each other (membranes with very little interior cytosol) and this is where the molecules needed for visual transduction are located.





Inner segment Which has the cellular organelles (mitochondria, Golgi, peroxisomes, lysosomes, etc.).

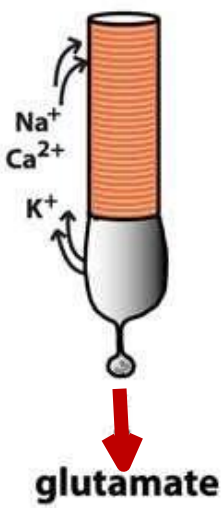
Release NTs (glutamate)

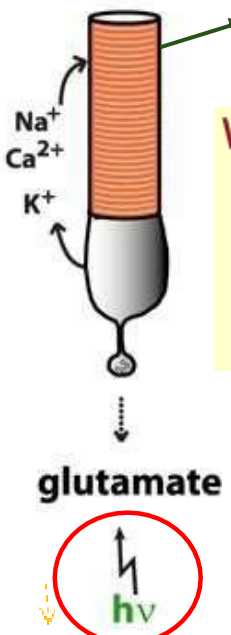
The dark current

Rods and cones act in an opposite fashion of what a typical neuron does. Instead of being in an RMP state at rest, they'll be in a depolarized state where they continuously release glutamate. So, they're actually active at rest.

1. Most neurons maintain a resting membrane potential (-60 to -70 mV). When excited, they open cation channels causing depolarization and opening of voltage-gated Ca^{2+} channels at the synapse. Ca^{2+} ions flow in and promote the fusion of synaptic vesicles, which release neurotransmitters.
2. Rods and cones work "backwards". At rest (in darkness), rods and cones are depolarized to -35 to -45 mV.

1. At dark, Na^+ and, to a lesser amount, Ca^{2+} enter through cyclic nucleotide-gated channels in the outer segment membrane.
2. K^+ is released through voltage-gated channels in the inner segment.
3. Rod cells are depolarized.
4. The neurotransmitter glutamate is released continuously.





The signal is the **low** release of the neurotransmitter glutamate

When excited:
1. Channels in the outer segment membrane close
2. Rod cells hyperpolarize, and
3. Glutamate release decreases.

But once light photons hit them, they will undergo hyperpolarization due to closing of calcium channels and this results in decreased secretion of glutamate.

This explanation is at the cellular level

Generation of the visual signal

At a molecular level

The players 5 Molecules

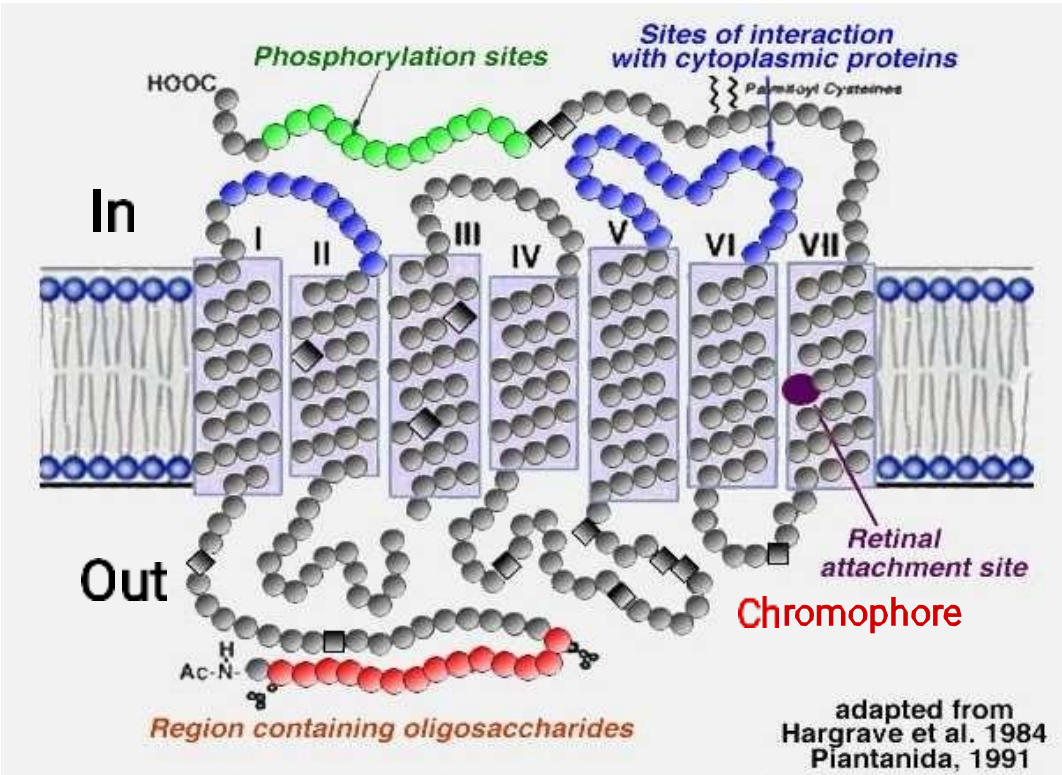
- Rhodopsin (opsin + pigment molecule) → Rhodopsin is considered a holoprotein, meaning it consists of a protein "apoprotein" component (the opsin) and a non-protein "prosthetic group" component (the pigment 11-cis retinal).
- Transducin
- Phosphodiesterase
- Na^+-gated channels
- Regulatory proteins

Rhodopsin

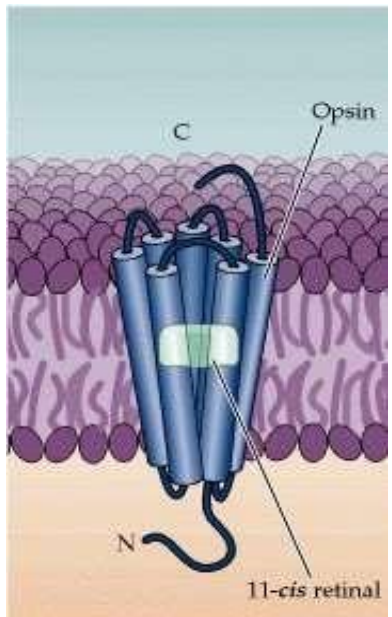
7-transmembrane domain receptor (it's a GPCR) with both cytosolic and extracellular domains.

Opsin is a single polypeptide chain with seven helical segments that span the membrane.

The amino acid sequence here is very important, as cone cells will end up having different transmembrane domains (within their receptors) but will still have the same chromophore.



15-20% of proteins in our genome are membrane proteins; most of them have a single transmembrane domain, followed by the 7-transmembrane domain receptors.



The chromophore is what absorbs light, and it's found at the 7th transmembrane domain S7.

The paper dr was talking about

Estimation of Membrane Proteins in the Human Proteome

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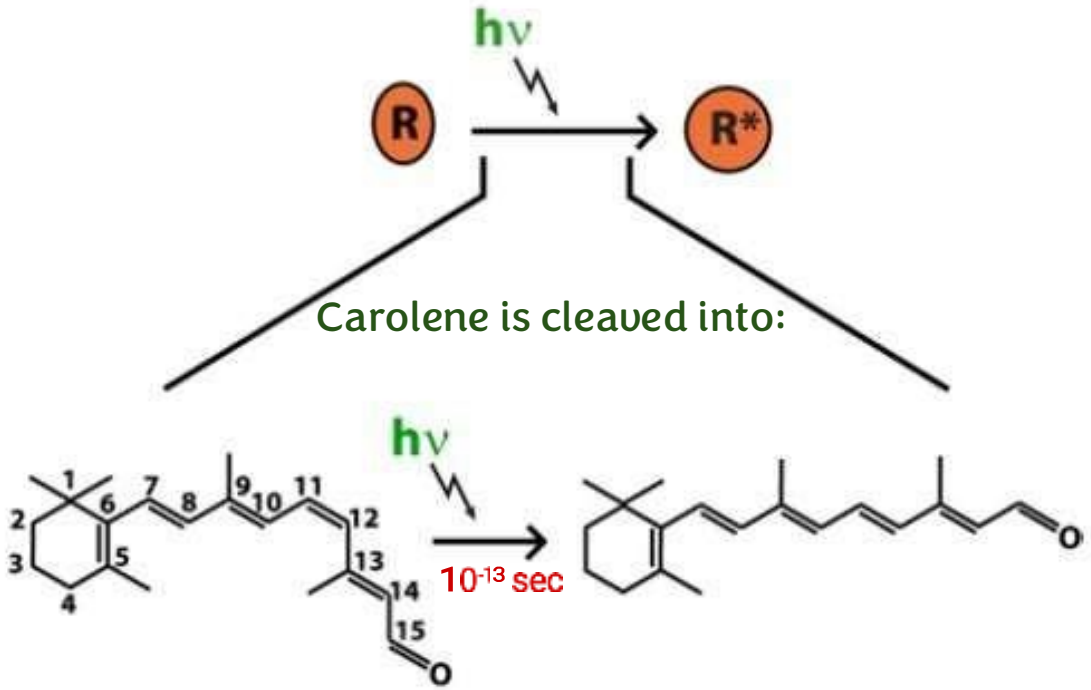
ABSTRACT: Genomics and proteomics have added valuable information to our knowledgebase of the human biological system including the discovery of therapeutic targets and disease biomarkers. However, molecular profiling studies commonly result in the identification of novel proteins of unknown localization. A class of proteins of special interest is membrane proteins, in particular plasma membrane proteins. Despite their biological and medical significance, the 3-dimensional structures of less than 1% of plasma membrane proteins have been determined. In order to aid in identification of membrane proteins, a number of computational methods have been developed. These tools operate by predicting the presence of transmembrane segments. Here, we utilized five topology prediction methods (TMHMM, SOSUI, waveTM, HMMTOP, and TopPred II) in order to estimate the ratio of integral membrane proteins in the human proteome. These methods employ different algorithms and include a newly-developed method (waveTM) that has yet to be tested on a large proteome database. Since these tools are prone for error mainly as a result of falsely predicting signal peptides as transmembrane segments, we have utilized an additional method, SignalP. Based on our analyses, the ratio of human proteins with transmembrane segments is estimated to fall between 15% and 39% with a consensus of 13%. Agreement among the programs is reduced further when both a positive identification of a membrane protein and the number of transmembrane segments per protein are considered. Such a broad range of prediction depends on the selectivity of the individual method in predicting integral membrane proteins. These methods can play a critical role in determining protein structure and, hence, identifying suitable drug targets in humans.

KEYWORDS: Membrane proteins, human, proteome, transmembrane segment, bioinformatics, prediction, proteomics, waveTM, TMHMM, HMMTOP, SOSUI, TopPred II, SignalP

The chromophore (11-cis-retinal)

From vitamin A

We can't really synthesize vitamin A, so we can only get it from diet (without vitamin A, we can't get the pigment 11-cis-retinal).



11-*cis* retinal

The double bond between carbon number 11 and 12 is in the cis orientation.

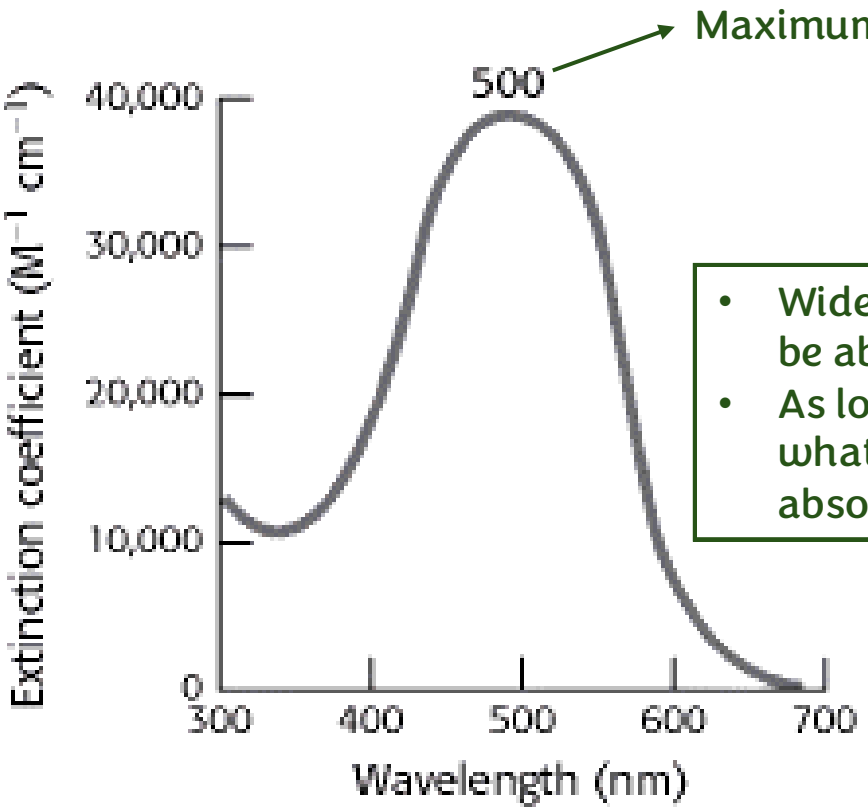
all-*trans* retinal

When light hits the double bond, it'll change it into the trans orientation.

- The conversion here from cis to trans is incredibly fast (~100 fm), and it's considered to be the fastest change in double bond structure in organic chemistry at that time.
- Now, all the double bonds are in the trans orientation, causing a change in the structure of the rhodopsin molecule.

https://www.nobelprize.org/prizes/medicine/1967/wald/facts/

Light absorption by rhodopsin

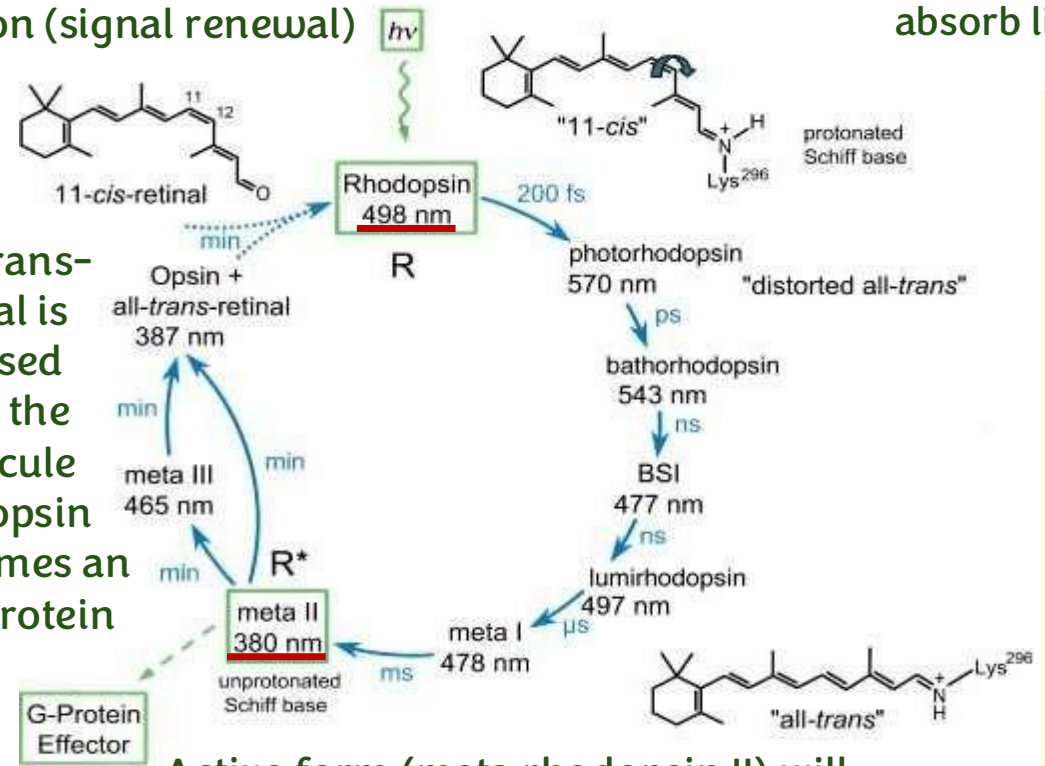


- Wide range of wave lengths of light will be absorbed by 11-cis retinal
- As long as there's some overlap between what the bulb emits and what rhodopsin absorbs, you'll see something

Rhodopsin intermediates

As we know, the rhodopsin will reach its maximum absorption at a wavelength of 500nm. When it absorbs light, it uses this electromagnetic energy in changing the bond configuration and its overall conformation too resulting in different rhodopsin structure (intermediates) Each intermediate will absorb light at a different wavelength

Rhodopsin can then bind to another 11-cis-retinal to be able to take in another photon (signal renewal)



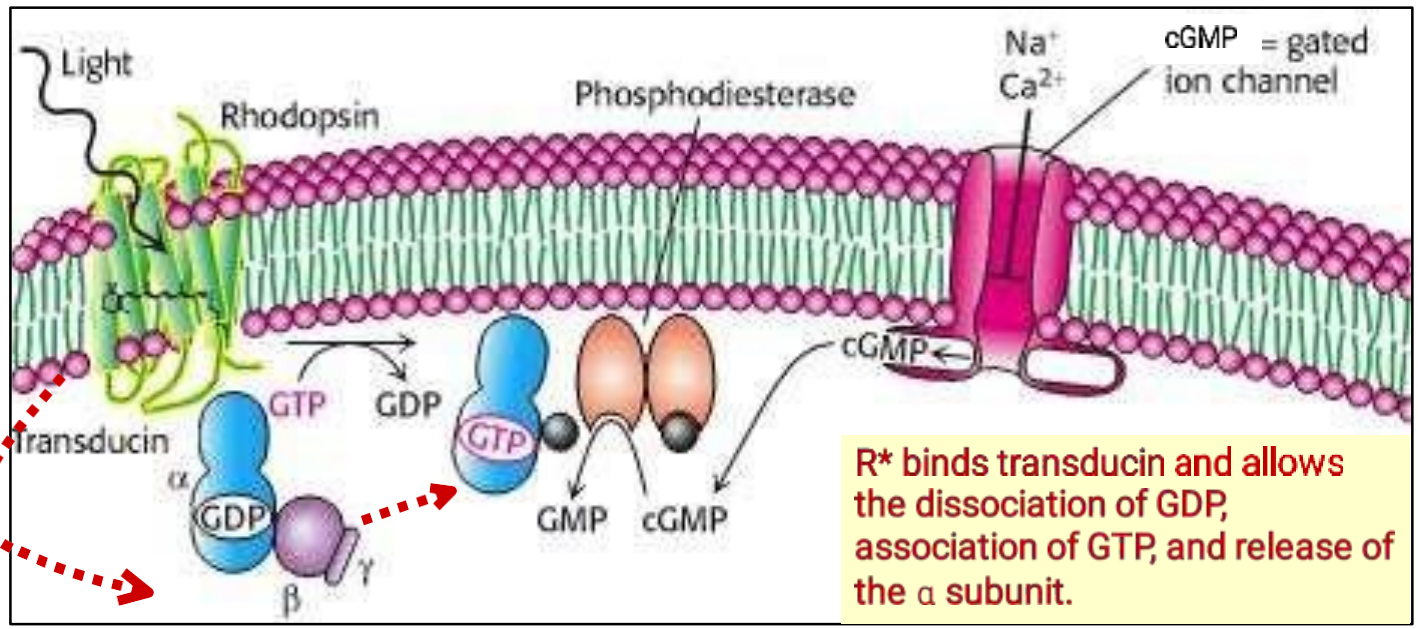
All-trans-retinal is released from the molecule and opsin becomes an apoprotein

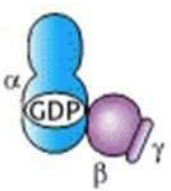
Active form (meta rhodopsin II) will transmit the signal into the G-protein

- By itself, 11-cis retinal absorbs near UV light. But opsin changes the distribution of the electrons exciting its electrons with less energy (i.e., longer wavelength light).
- The chromophore converts the energy of a photon into a conformational change in protein structure.
- Rearrangements in the surrounding opsin protein convert it into the active R* state, an intermediate known as metarhodopsin II.

Transducin → Phosphodiesterase (PDE)

The G protein here is called "transducin."



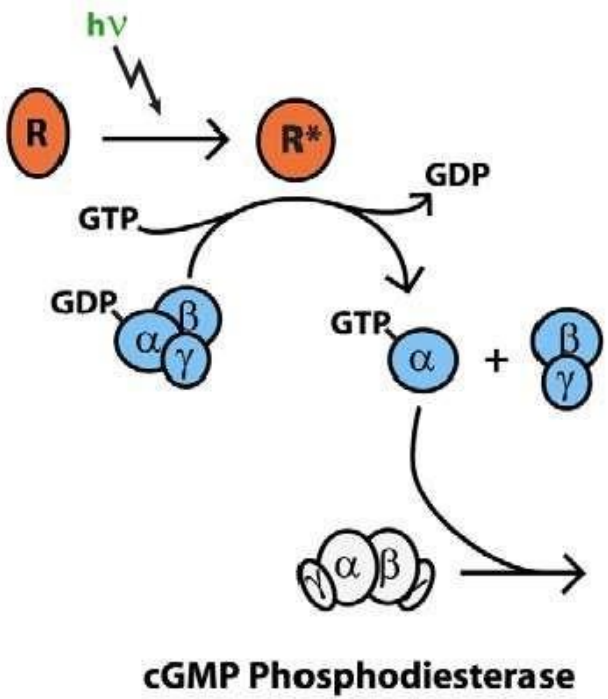


G proteins are heterotrimeric, consisting of α, β, and γ subunits. In its inactive state, transducin's α subunit has a GDP bound to it.

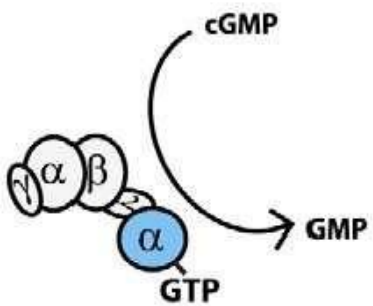
- The intermediate meta II activates transducin, this interaction will cause the GDP bound to the alpha subunit to be released and replaced with a GTP, which activates the alpha subunit to be released.
- GTP-bound alpha will interact with the cGMP phosphodiesterase that converts cGMP to GMP.
- There are ion channels here that depend on cGMP binding to be activated to open. This reaction by PDE will decrease the intracellular cGMP levels, leading to the closing of ion channels, stopping the entry of Na^+ and Ca^{2+}(hyperpolarization)

Dark → opened (cGMP is bound to the channels & cations enter easily)
Light → closed (less cGMP due to PDE activity so cations cannot get into cells)

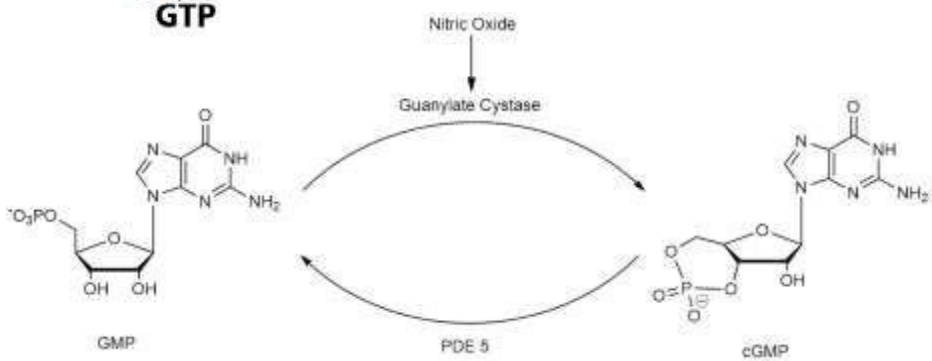
Activation of phosphodiesterase



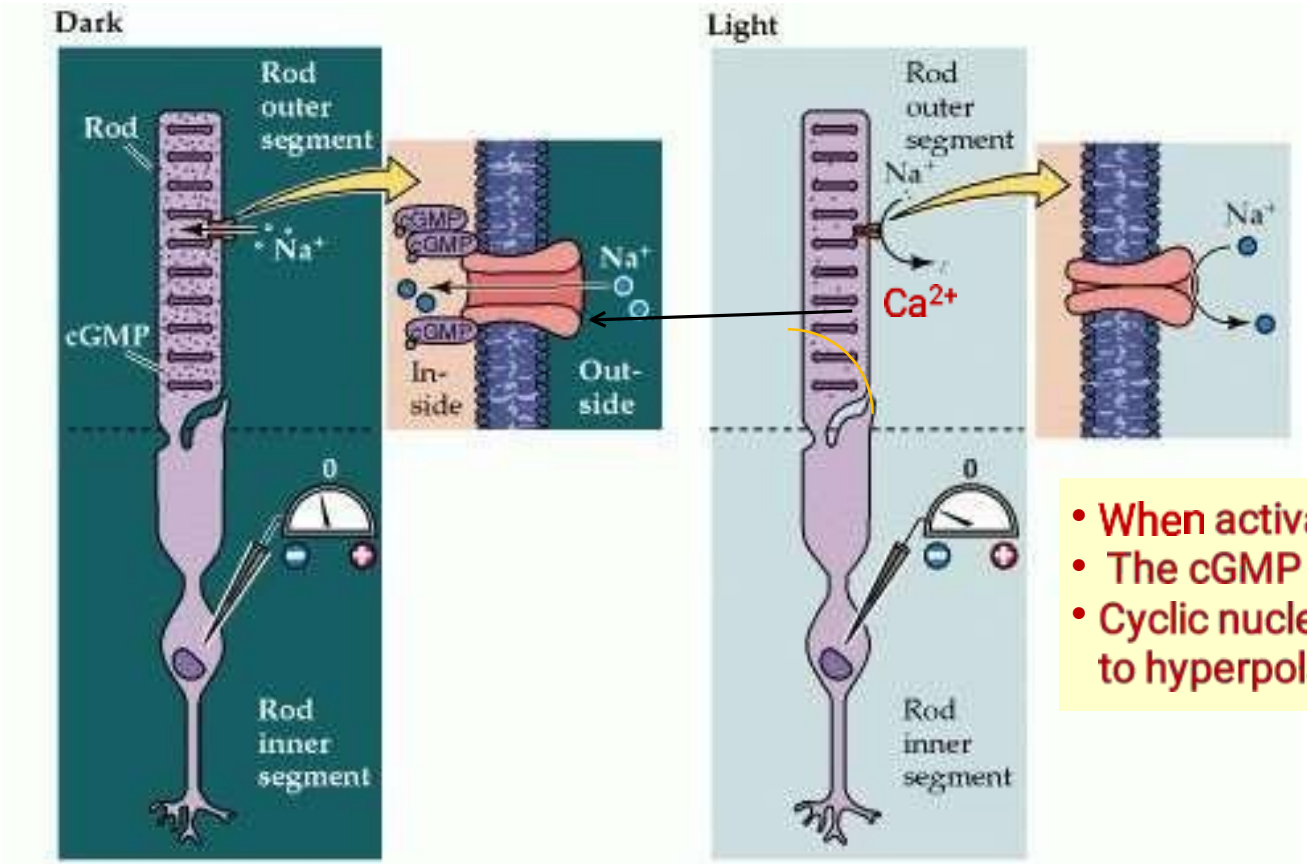
- PDE is a heterotetramer that consists of a dimer of two catalytic subunits, α and β subunits, each with an active site inhibited by a PDE γ subunit.
- The activated transducin α subunit-GTP binds to PDE γ and relieves the inhibition on a catalytic subunit.



- cGMP is synthesized from GTP through the enzyme **guanylate cyclase** (similar to adenylate cyclase) & cGMP is converted to GMP by the **cGMP PDE** (activated by transducin)



cGMP-gated channels

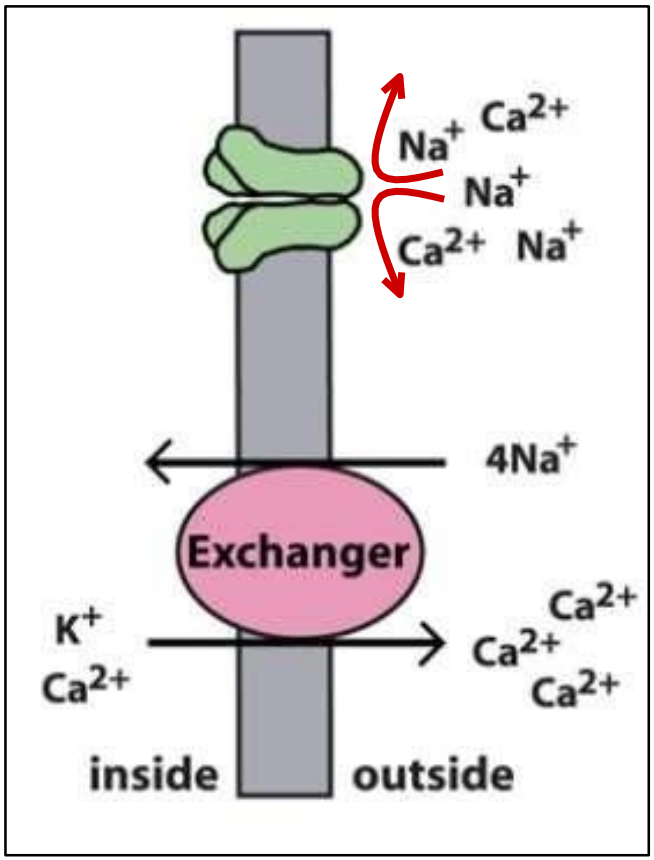


Summary

- Dark current → increase of cGMP levels → keeps channels open, and Na^+/Ca^{2+} will get into the cell.
- With light activation → cGMP will be turned into GMP through PDE, leading to channels closing and hyperpolarization.

- When activated, PDE hydrolyzes cGMP to GMP.
- The cGMP concentration inside the rod decreases.
- Cyclic nucleotide-gated ion channels close leading to hyperpolarization.

Levels of calcium ions are reduced, too.

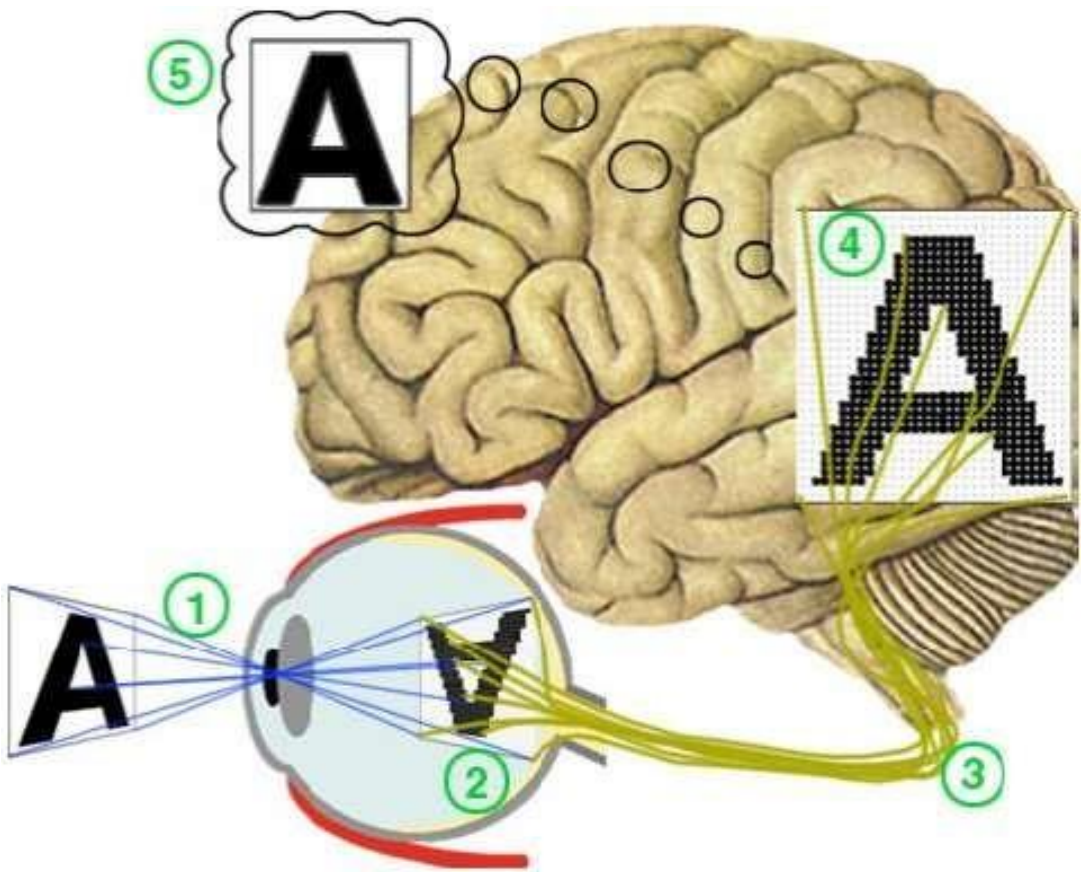


When the channels close, Ca^{2+} ceases to enter, but extrusion through the exchanger continues, so intracellular $[Ca^{2+}]$ falls.

$[cGMP]\downarrow \longrightarrow$ Ion channels closed $\xrightarrow[50\ nM]{500\ nM} [Ca^{2+}]\downarrow$

- Both cGMP and Ca^{2+} concentrations will decrease intracellularly. For calcium, it's due to the closing of ion channels + their efflux through an exchanger that allows sodium ions to enter & both calcium and potassium ions to exit → Change on the intracellular concentration of calcium ions from 500nM to 50nM.

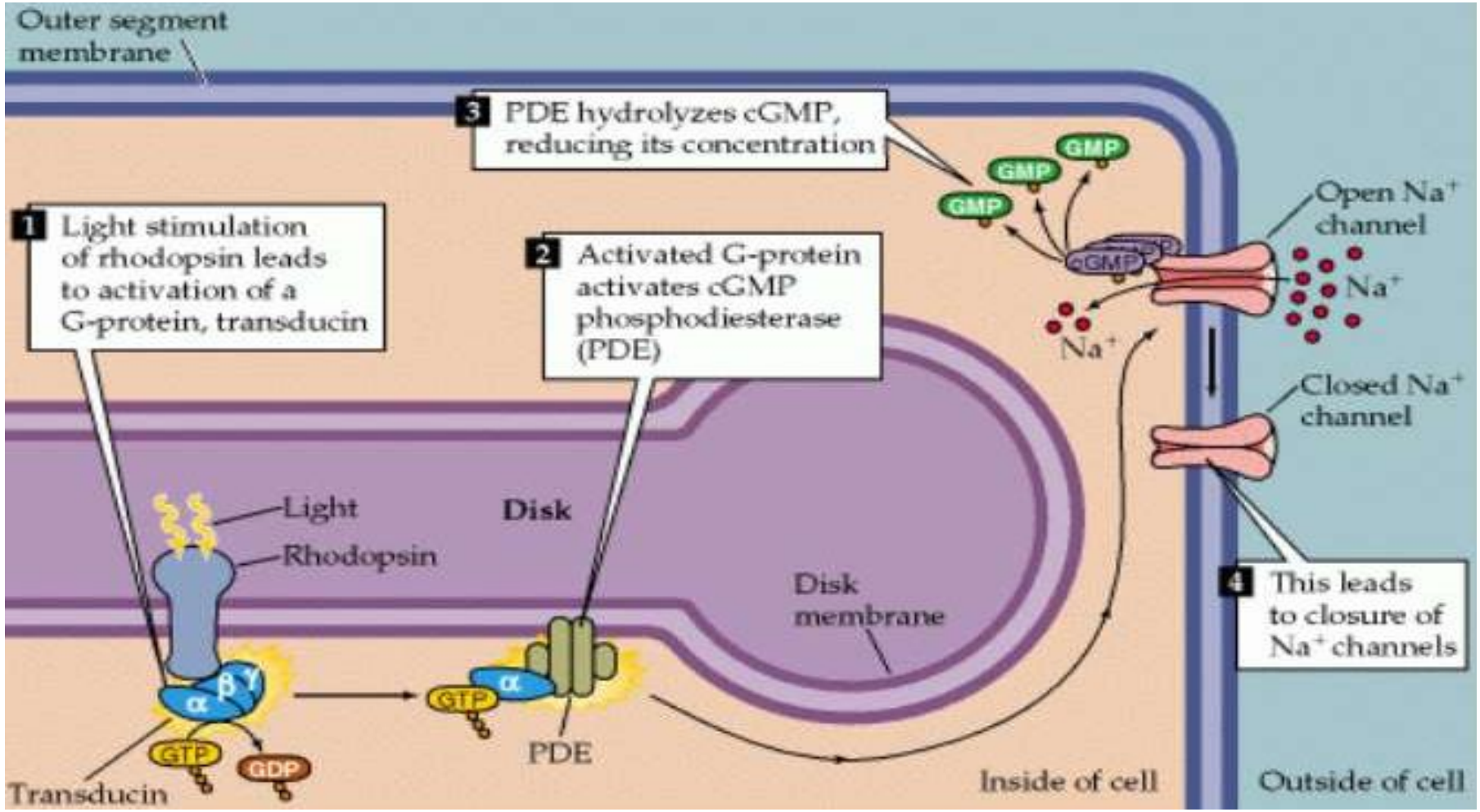
Creating an image



- The large potential difference travels as an electrical impulse down the rod cell to the synaptic terminal and is then transferred to an adjoining nerve cell.
- The nerve cell carries this impulse all the way to the brain.
- The brain then determines where the nerve impulse originated and interprets the image.

Eventually, the optic nerve will transmit the signal to the brain, which can form an image.

The overall pathway :



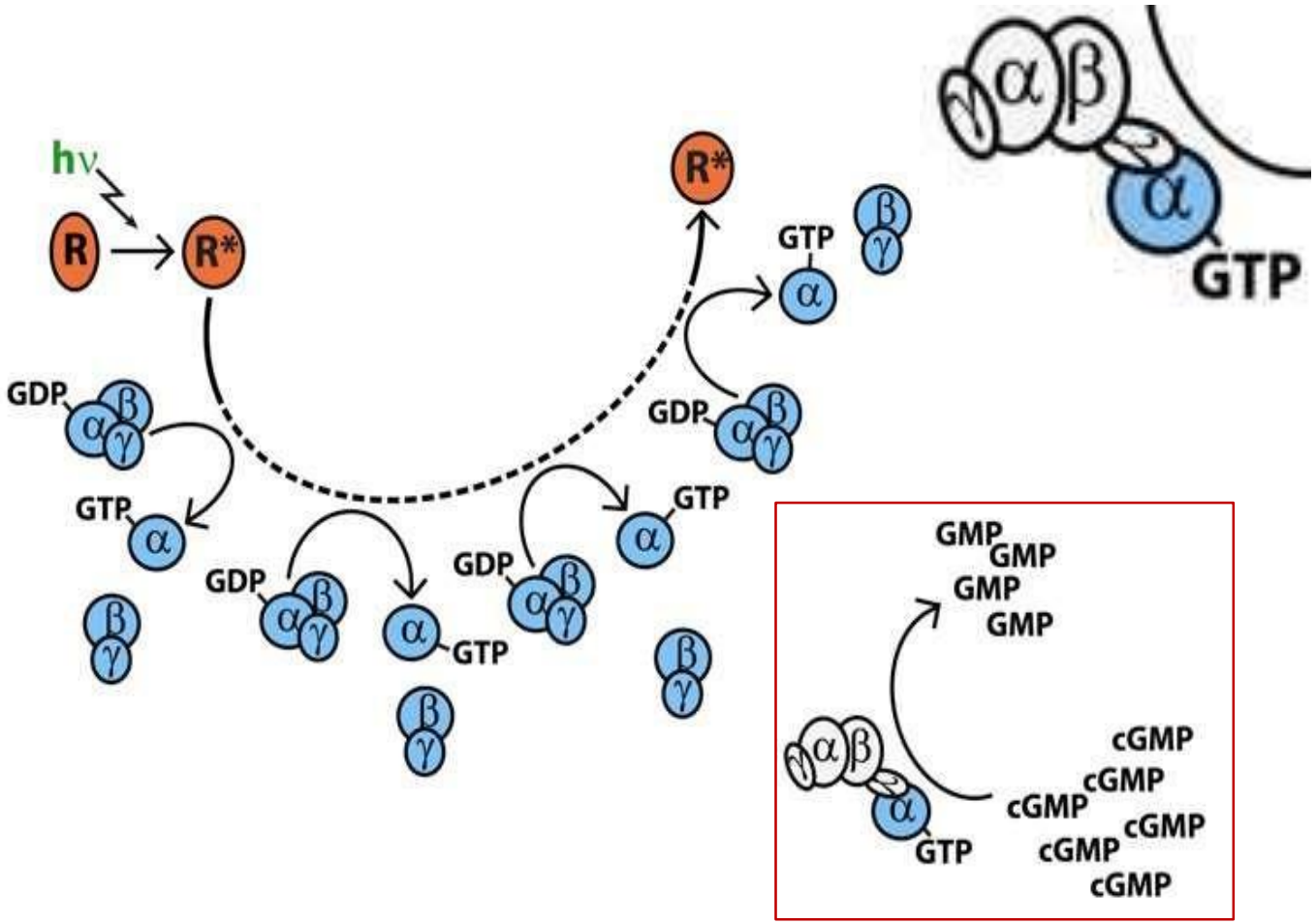
↓ Ca^{2+} concentration intracellularly will directly affect the release of the NT glutamate, as calcium is important in facilitating presynaptic vesicle fusion.

Signal amplification

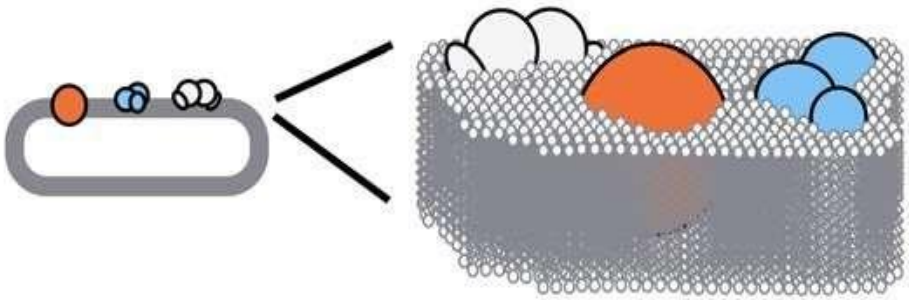
A little amount of photons (as little as one) can initiate a visual transduction signal.

Rhodopsin (1) → Transducin (10 to >3000) → Transducin (1) → PDE (1) PDE (1) → cGMP (10^3)

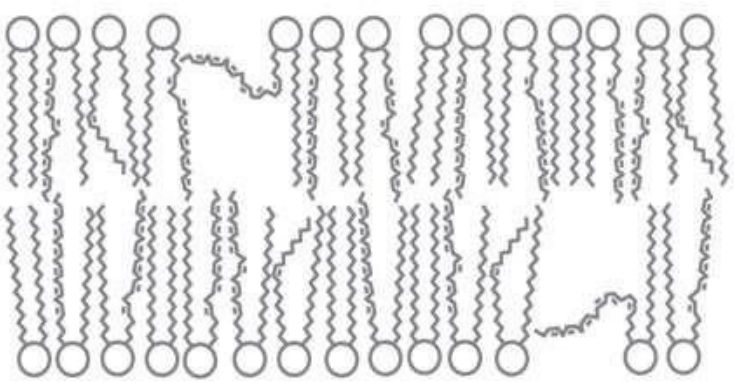
- We have thousands of rhodopsin molecules in each cell. Looking at one receptor, it can activate thousands of transducin molecules (signal amplification), while one transducin can only activate one PDE (1:1). PDE can break down thousands of cGMPs (amplification) and we just need a small amount of cGMP to be degraded for channels to be affected (cooperativity).



Facilitation of transduction



1. 2-dimensional surface: All of these molecular components are found in the plasma membrane, which limits them to 2D movement, and this increases the probability of their collision than if they were moving in 3D space.



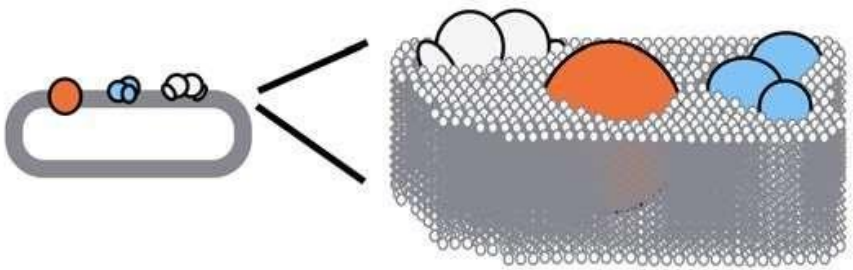
2. Low in cholesterol and high content of polyunsaturated, long-chain fatty acids: Having a high amount of polyunsaturated long-chain fatty acids causes the membrane to have an olive oil texture, making the proteins' movement far easier.

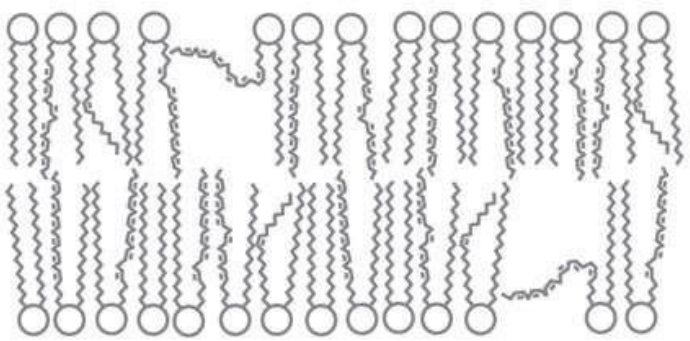
- *Deficiency in essential ω3 fatty acids leads to progressive retinal dystrophy*

Overall, a single photon closes about 200 channels and thereby prevents the entry of about million Na+ ions into the rod cells. Amplification

Next slide →

Facilitation of transduction





3. Cooperativity of binding: The binding of one cGMP enhances additional cGMP binding and channel opening (Hill coefficient n = ~3) → *amplification*

Cooperativity is measured in Hill coefficient, which tells us the degree of cooperativity that increases with the ratio. Here, cGMP channels have a higher cooperativity (~3) than hemoglobin (~2.6), making the signal transduction more efficient.

4. Since multiple cGMP molecules are required to open the channel, it will close when only one or two cGMP molecules leave the channel, making it easier to shut down by absorption of light.

Overall, a single photon closes about 200 channels and thereby prevents the entry of about million Na+ ions into the rod cells. Amplification

The cell functions like “a gold scale”, where any slight change can have a very large effect.

Signal termination

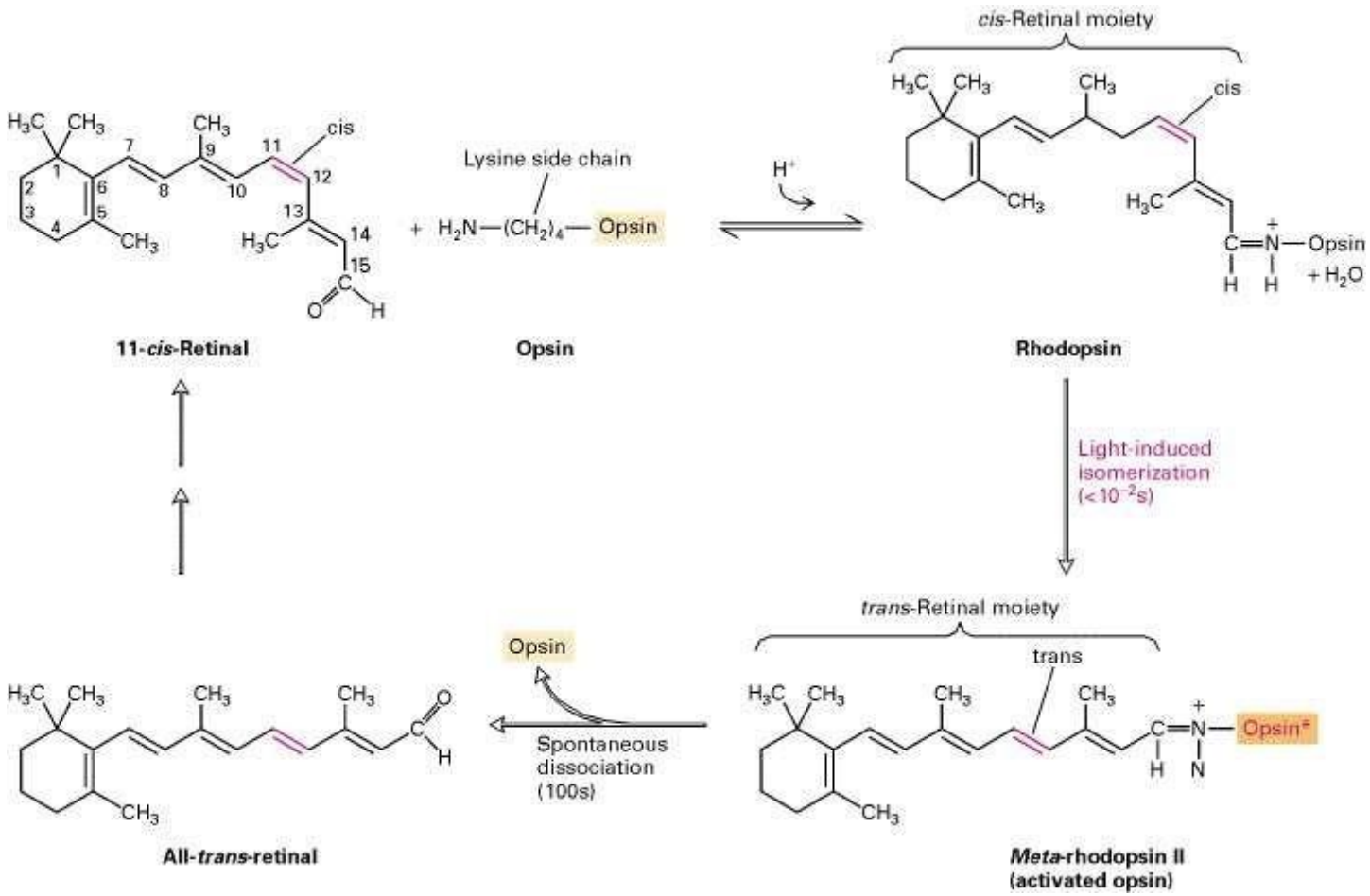
-Normally, signal is activated and immediately terminated allowing us to see the smooth continuous movement of a person.

-If the signal is not terminated, we would only see the final position of a person without the transition.

For example, without signal termination you will only see the two images to the right, the individual with their left arm up then their right arm-up, but you would not be able to see the smooth movements of the arm as it moves up or down. You would only see their final positions.

Mechanism I (The release of all-trans-retinal molecule).

Unstable all-trans rhodopsin complex



Explanation ↓

Mechanism I

Unstable all-trans rhodopsin complex

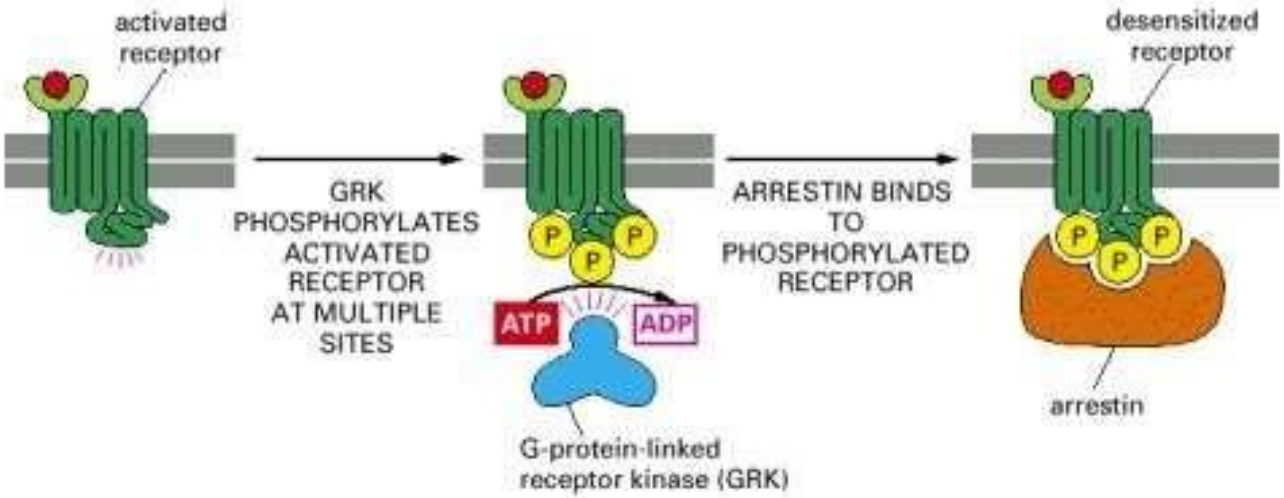
1) 11-cis-retinal absorbs light and becomes an all-trans molecule. This results in the changing of rhodopsin into meta-rhodopsin II.

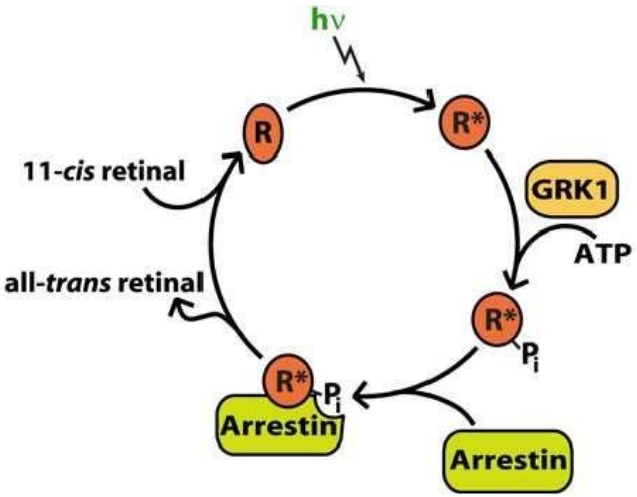
2) Interaction of the all trans-retinal molecule to opsin becomes **unstable**, resulting in the release of the all-trans molecule.

3) Therefore, the rhodopsin molecule becomes opsin and goes back to its inactive confirmation and cannot activate Transducins anymore.

4) All-trans-retinal becomes 11-cis-retinal which can bind to opsin to form rhodopsin once again.

Mechanism II
Arrestin binding





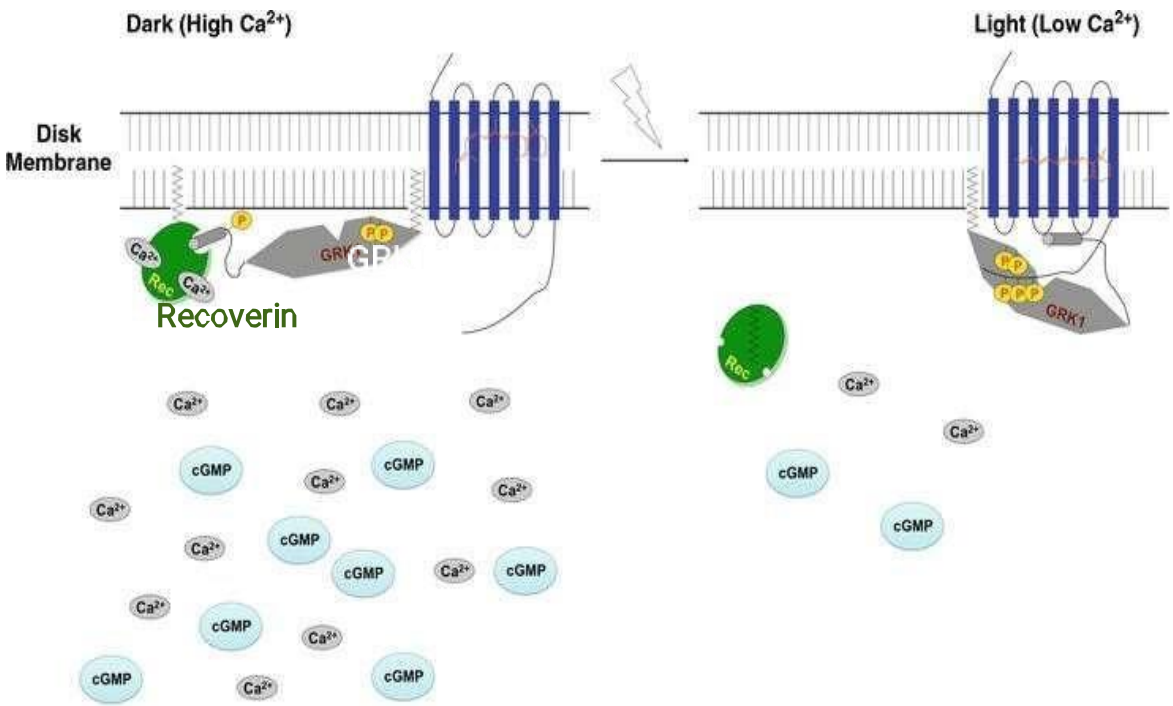
- Rhodopsin kinase 1 (GRK1) phosphorylates the C-terminus of R*. (R* or meta rhodopsin II = active rhodopsin)
- Phosphorylation of R* has two effects:
  1. It decreases transducin activation
  2. It facilitates binding to arrestin, which completely quenches its activity, and releases of the all *trans-retinal* regenerating rhodopsin. =Stops

"Phosphorylation **reduces** the efficiency of rhodopsin **&** arrestin binding leads to **total inactivation** of rhodopsin".

Mechanism II (cont.)
GRK1 and recoverin

-Recall that when the ion channels close (in the presence of light), not only the membrane hyperpolarizes, but there is also a reduction in the concentration of Ca^{2+}.

- GRK1 is more active at low [Ca^{2+}]. Why?
- In the dark, Ca^{2+} ions bind to a protein called recoverin allowing it to anchor to the membrane, bind to GRK1, and inhibit it.
- At low [Ca^{2+}], Ca^{2+}-free recoverin does not bind to GRK1. ⟶ Without this inhibition, the kinase is more active and can phosphorylate rhodopsin.

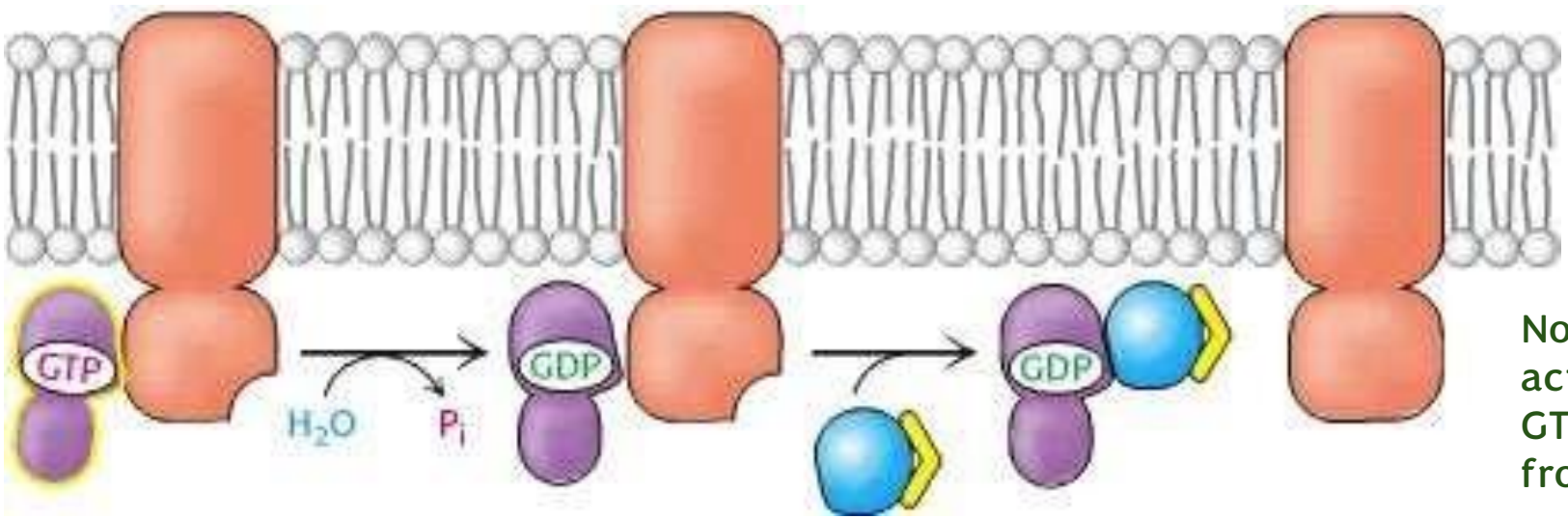


- *Ca^{2+}-Calmodulin (CaM) also binds to GRK1 and inhibits it.*

Basically: There are two proteins (**Recoverin** & **Calmodulin**) that can bind to the kinase GRK1 & inhibit it (at high [Ca^{2+}]).
Both are regulated by Ca^{2+}.

Mechanism III

Intrinsic GTPase activity of G protein



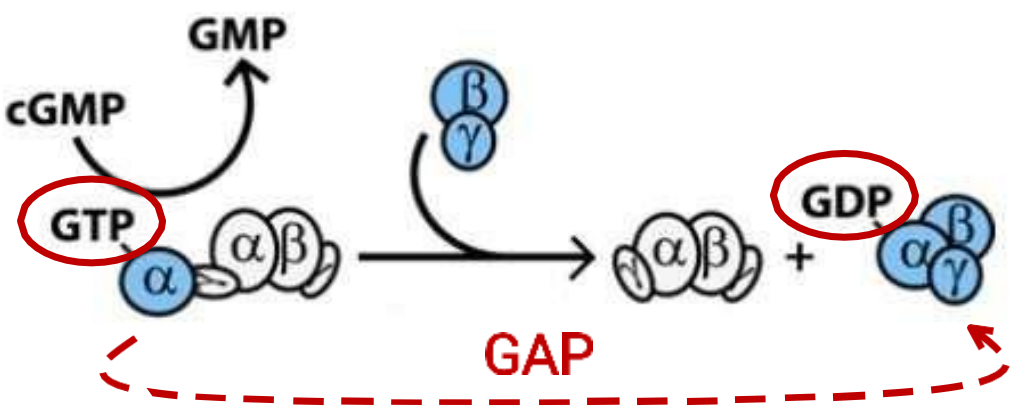
Note that; GTPase activity increases as GTP– α is released from Transducin.

- Gα (of Transducin) has an intrinsic GTPase activity that hydrolyzes GTP to GDP. **Therefore, the protein inactivates itself.**
- Upon hydrolysis of GTP to GDP, transducin α subunit releases the PDE γ subunit that re-inhibits the catalytic subunit.
- Transducin α-GDP eventually combines with transducin βγ.

Mechanism IV

Facilitation of GTPase activity of G protein

- GTP hydrolysis is slow intrinsically, but it is accelerated by a GAP (GTPase-activating protein) complex.
  - To ensure that transducin does not shut off before activating PDE, transducin and the GAP complex have a low affinity for each other, until transducin α-GTP binds PDEγ.



There is a period in which transducin α-GTP is allowed to bind to the phosphodiesterase (so it can perform its function), and after that, the GAP complex can bind to the alpha subunit and activate its intrinsic GTPase activity.

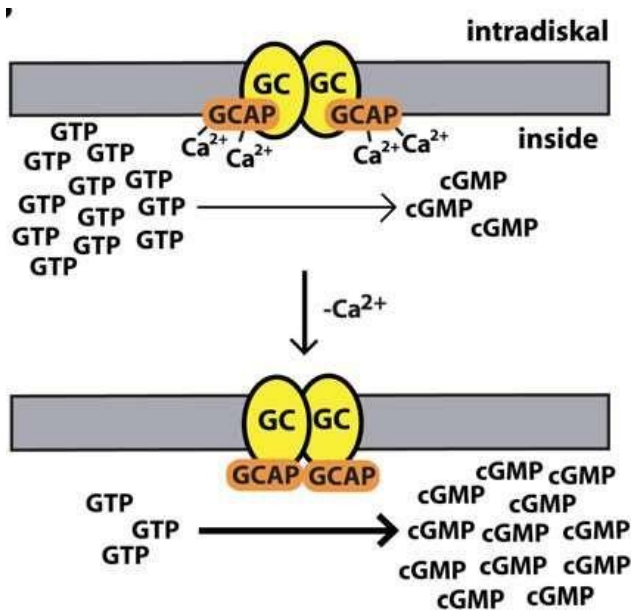
The inhibition of the Gα subunit by GTP hydrolysis and, hence, dissociation from PDE is the rate-limiting step in the recovery of rod response to light.

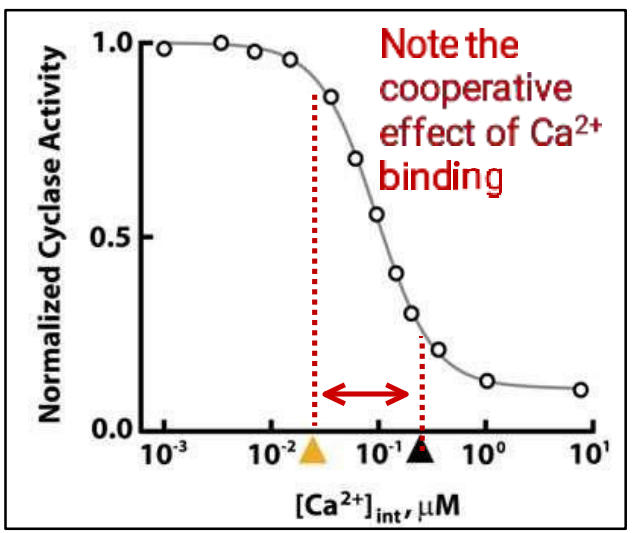
This is the important step in facilitating (speeding up) visual transduction.

Mechanism V Feedback regulation

Guanylate cyclase

- Guanylate cyclase is an enzyme that converts GTP into cGMP.
- **Guanylate cyclase-activating proteins (CGAPs) are activators of guanylate cyclase.**
- **In the dark, CGAPs bind Ca^{2+} and get inhibited, so they cannot activate GCs.**
- **A decrease of intracellular Ca^{2+} ions causes them to be released from CGAPs, which can then activate GC.**





Mechanism V Feedback regulation

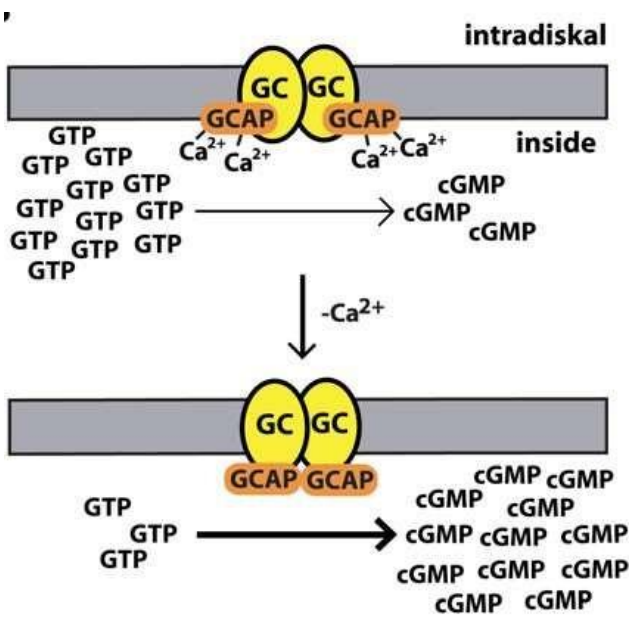
Guanylate cyclase

Recall from slide 21
Dark → increase of cGMP levels
→ keeping channels open

Light → decrease of cGMP levels
→ closing the channels

In the dark

There is a high level of Ca^{2+}, guanylate cyclase activating proteins (GCAPs) can bind to Ca^{2+}, blocking their activation of guanylate cyclase .
So, the amount of cGMP produced by guanylate cyclase would be low but enough to bind to channels to keep them open.



In the light Initially the channels are closed upon activation

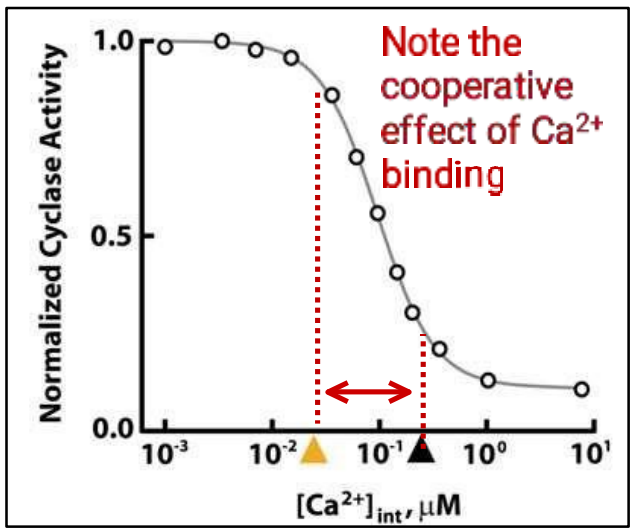
Ca^{2+} concentration decreases, Ca^{2+}dissociates from GCAPs. GCAPs can now activate guanylate cyclase leading to cGMP production in large amounts as a sort of a **feedback**, then cGMP binds to the channels opening them again and terminating the signal transduction.

Mechanism V

Guanylate cyclase

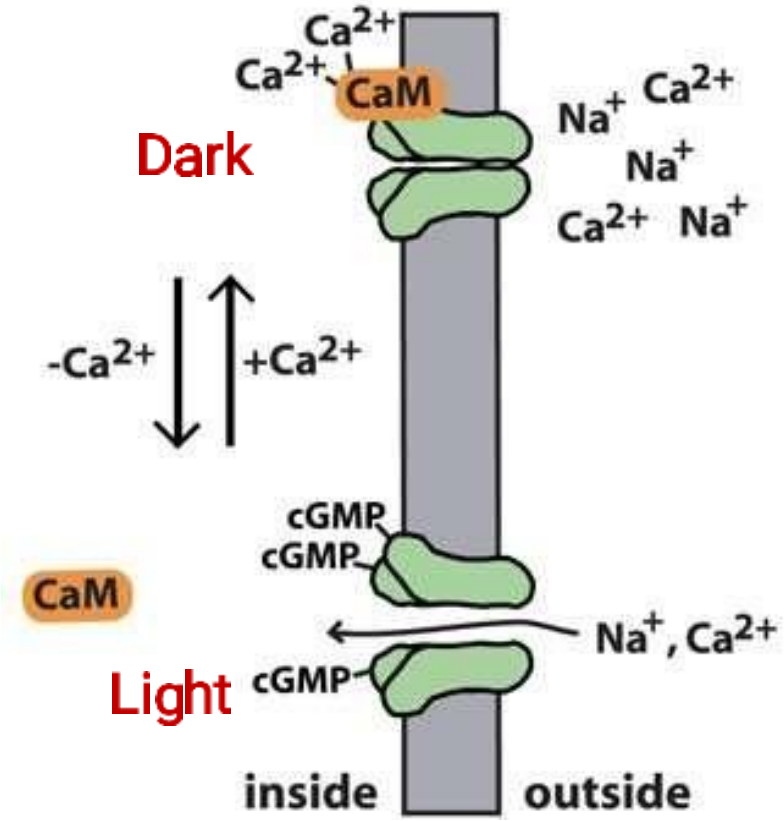
The graph is **sigmoidal** in shape meaning that we have two forms of the enzyme: the active form and the inactive form, and the transition between them is really quick → the binding of Ca^{2+} is **cooperative**.

As you can see in the graph, the activity of guanylate cyclase is highly sensitive to the level of calcium ions. Any reduction in the concentration of calcium ions leads to high activity of guanylate cyclase.



Mechanism VI Feedback regulation

Ca-calmodulin *and cGMP-gated channels*



In the dark CaM balance things out by keeping **some** of the channels closed.

- In the dark, Ca^{2+}-Calmodulin (CaM) binds the channel and reduces its affinity to cGMP and shuts it down.
- During visual transduction, the decrease in intracellular [Ca^{2+}] causes CaM to be released, the affinity towards cGMP increases, and the channel reopens in response to the slightest increase to cGMP.

- *Note: Ca^{2+}-Calmodulin (CaM) also binds to GRK1 and inhibits it.*

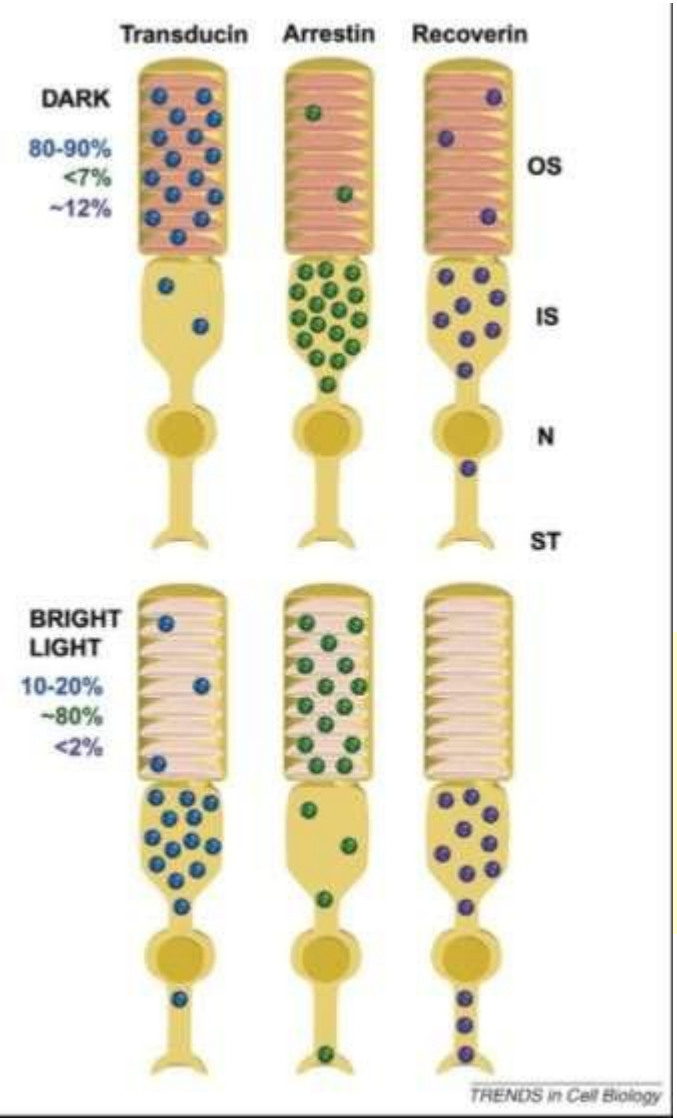
Note:
Every thing included in signal transduction and termination applies to this topic.

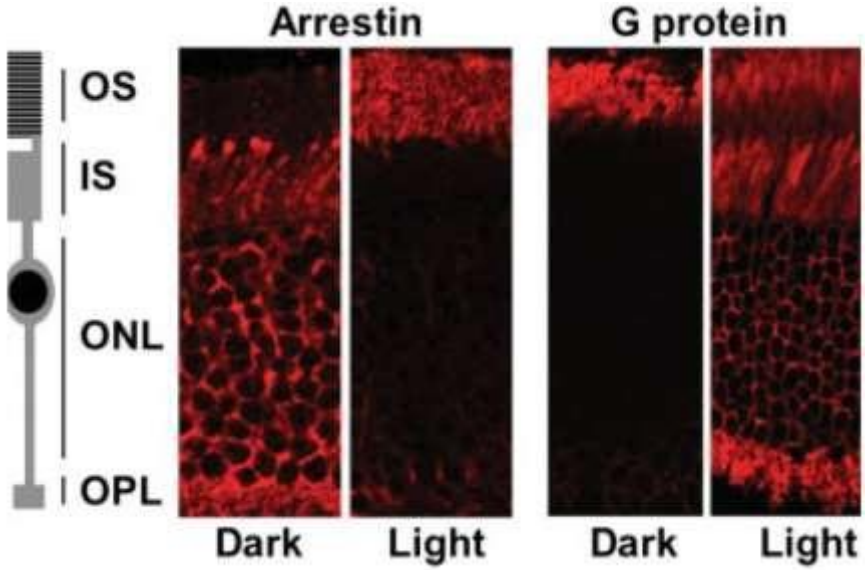
Adaptation to light/dark conditions

- You've probably noticed that if you move from a well-lit room into a dark room, you can't see anything at first as it takes some time for you to be able to see something.

- The opposite is true as well, if you move from a dark room to a well-lit room, your eyes are very sensitive at first, and it takes some time for you to be able to see clearly and for your eyes to relax.

Arrestin/recoverin/transducin distribution





- In dark, the outer segment contains high levels of transducin and recoverin and low levels of arrestin (low inhibition; ready to be activated).
- In light, it is the opposite (high inhibition; ready to be inactivated).

Arrestin/recoverin/transducin distribution

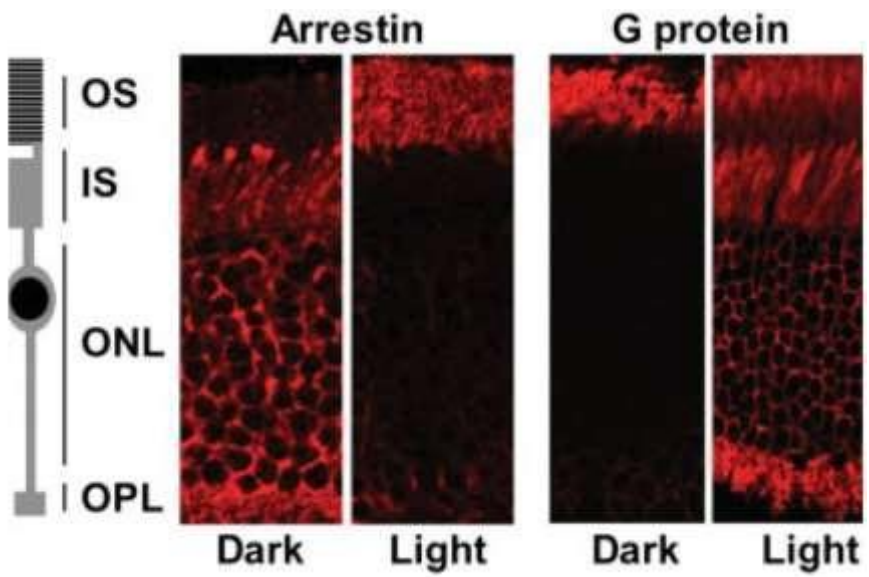
- As we can see in the image, the proteins Arrestin and G protein (Transducin) were labelled in a rod cell for an experiment.

- What was found is that in the dark **Arrestin** stays in the inner segment of the rod cell. On the other hand, with light it is localized in the outer segment.

- **Transducin and Recoverin** have the opposite behavior. In the dark they are localized in the outer segment and in light it is mainly localized in the inner segment.

Arrestin -> signal termination (inhibition of rhodopsin).

Recoverin -> binds to the kinase (GRK1), inhibiting its phosphorylation of rhodopsin making rhodopsin **ready to be activated.**



Arrestin/recoverin/transducin distribution

- **So why is this the case?**

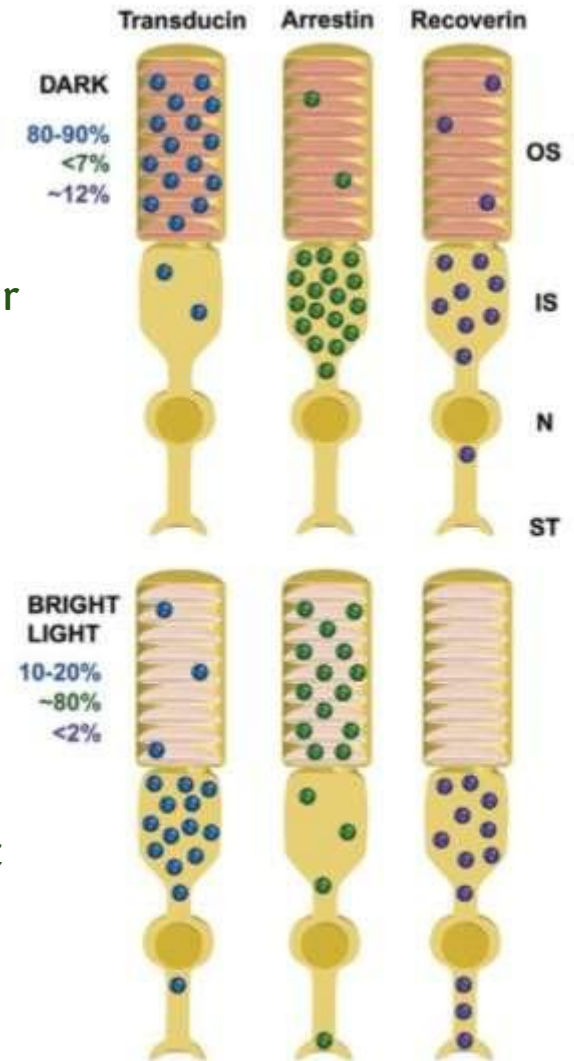
- When it's **dark**, you want **Arrestin** to stay in the **inner** segment to lower inhibition of rhodopsin and to have the rod cell very sensitive to any light. On the other hand, **transducin** is localized in the **outer** segment waiting for any signal (any photon to hit rhodopsin) so it can be activated.

- **Why does adaption take time?**

- In the case of adapting to light, **Arrestin** will slowly move from **the inner segment to the outer segment** in order to terminate the signal.

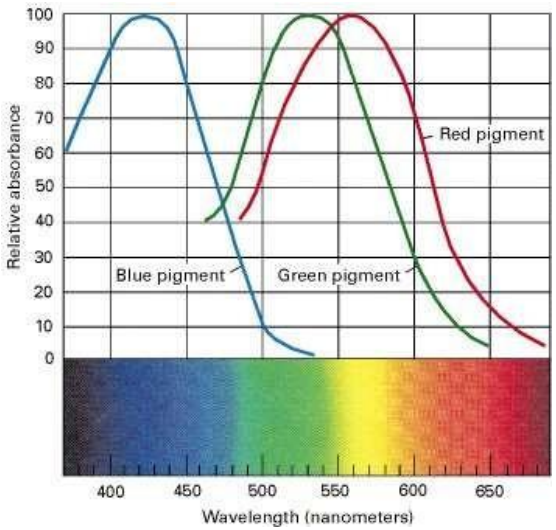
- **Transducin** will also have to move from **the outer segment to the inner segment** so that the signaling in rod cells is terminated.

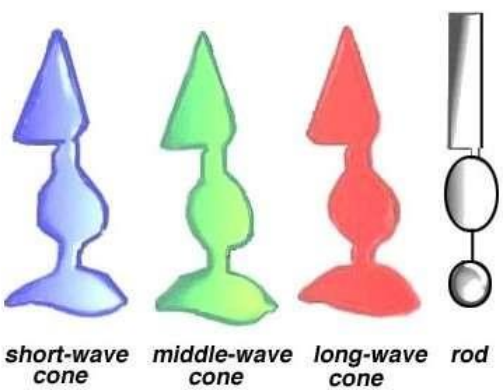
- **Recoverin** will have to move from **the outer segment to the inner segment** leading to its release from the kinase (GRK1) allowing it to phosphate rhodopsin and allowing arrestin to bind to the phosphorylated rhodopsin.

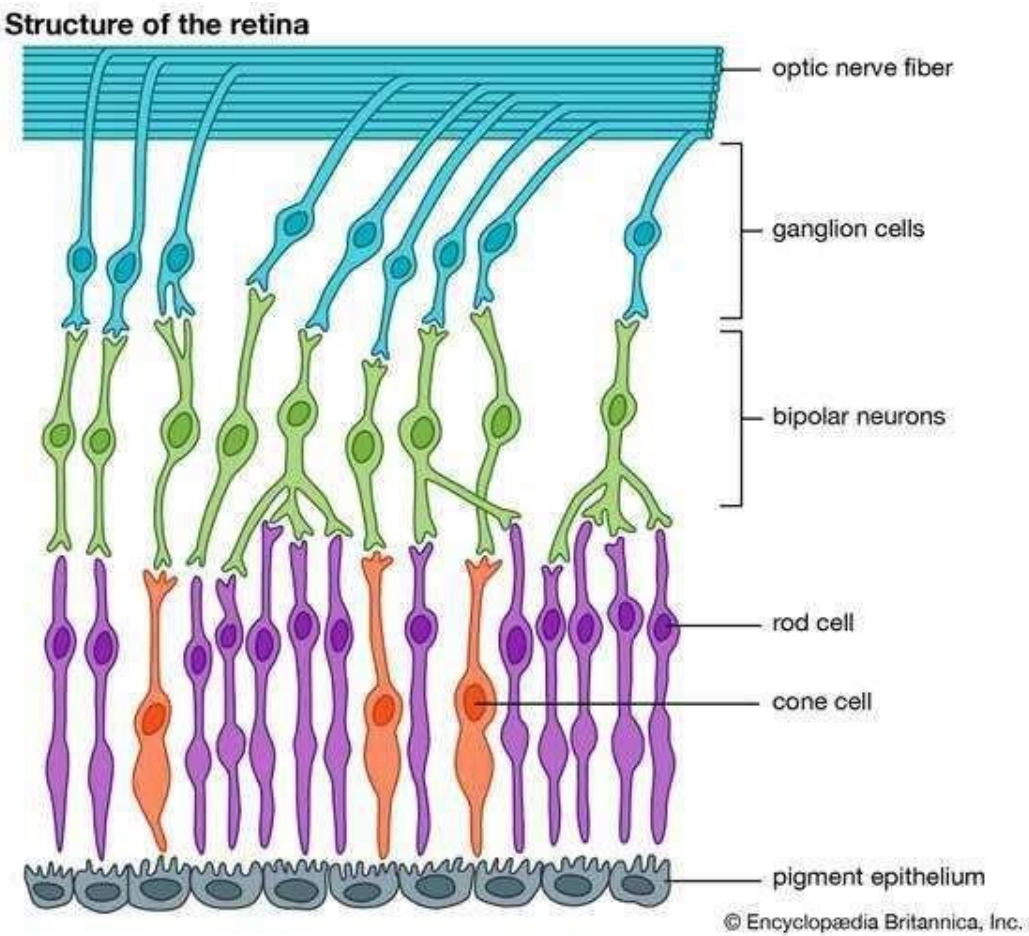


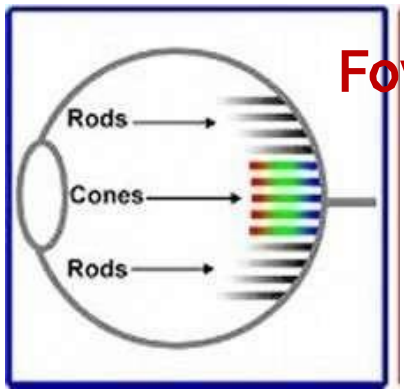
Color vision

Cone photoreceptor proteins

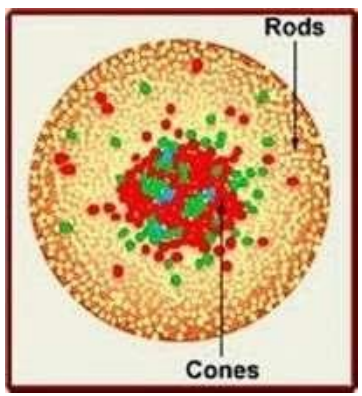








Fovea



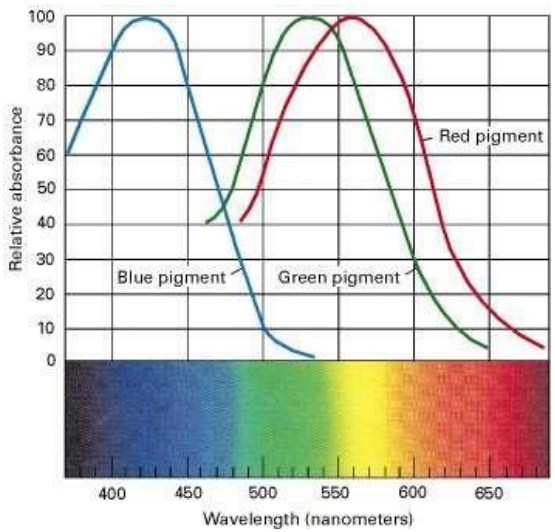
Cone photoreceptor proteins

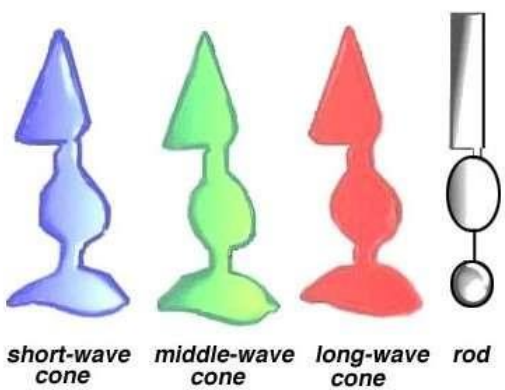
Cone cells are responsible for vision in **bright light**. There are three types of cone cells, each responsible for vision of a certain wavelength.

- **Short-Wave Cone (blue)**: Registers the shorter wave-lengths and has a peak for blue color vision.
- **Middle-Wave Cone (green)**: Responsible for visualizing the color green.
- **Long-Wave Cone (red)**: Responsible for visualizing the color red.

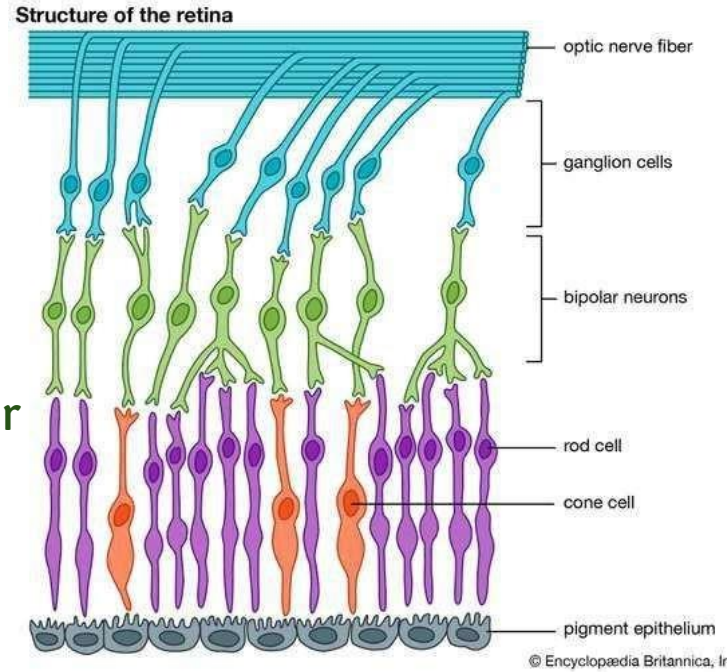
The combination of the three types of cones gives us color vision.

-Notice that green and red peaks are close to each other.





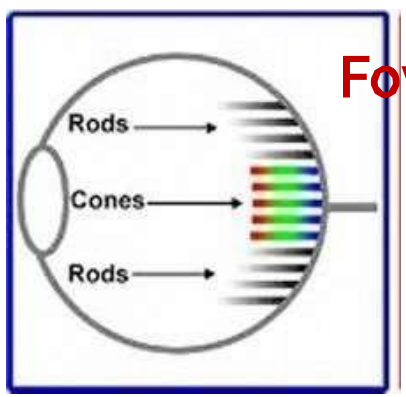
Cone photoreceptor proteins



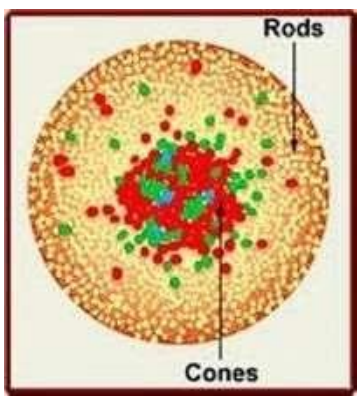
Cone cells are embedded within a larger population of rod cells.

One **difference** that should be noted between cone & rod cells is that multiple rod cells can connect to a single neuron. On the other hand, each cone cell is connected to a single neuron by itself.

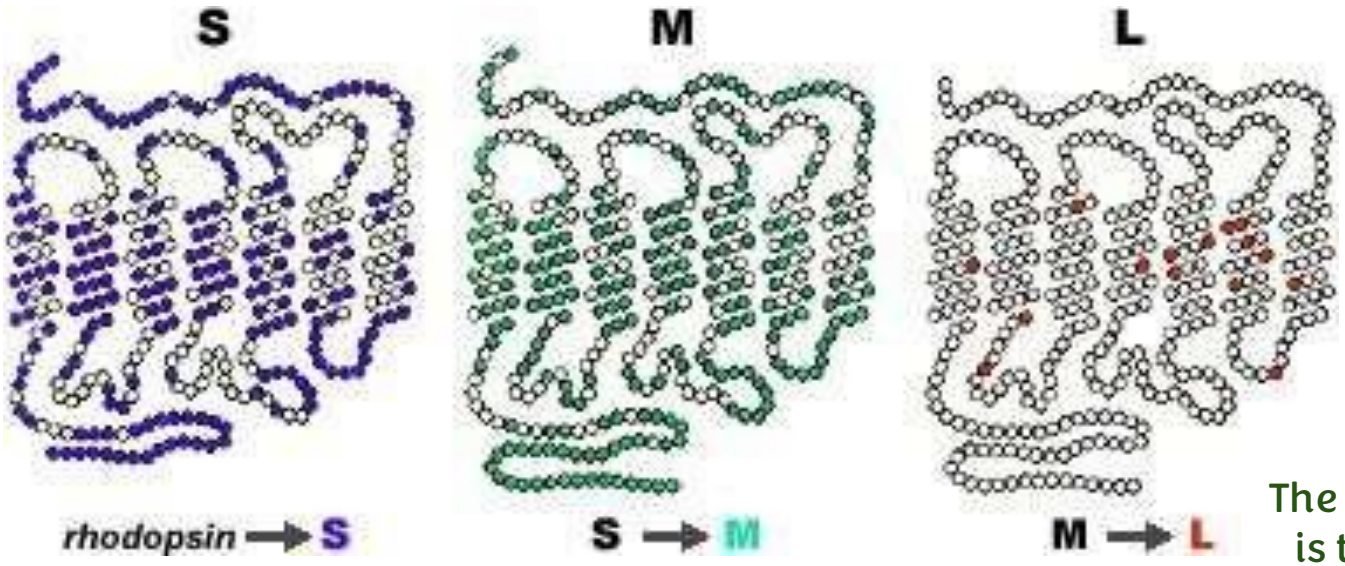
- Another **difference** between cone and rod cells is their location in the retina;
- Rod cells are scattered so they can absorb the photons from different angles.
- Cone cells are concentrated in a region called **Fovea**, as the bright light's photons are already condensed.



Fovea



How different are they?



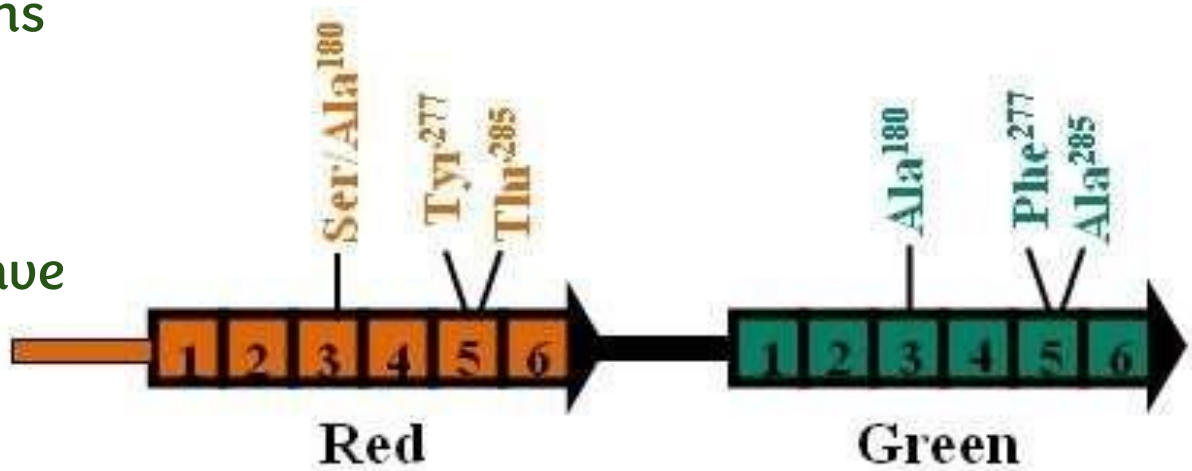
The chromophore (11-cis-retinal) is the same in rods and cones.

- Cone opsins (AKA, photopsins) have similar structures as rhodopsin, but with different amino acid residues surrounding the bound 11-cis retinal; thus, they cause the chromophore's absorption to different wavelengths.
- Each of the cone photoreceptors vs. rhodopsin ≈ 40% identical.
- The blue photoreceptor vs. green and red photoreceptors = ≈ 40% identical.
- The green vs. red photoreceptors > 95% identical. This is why their peaks are close to each other.

Three important aa residues

There are three important amino acids that differ between the red and green photoreceptors. They are in positions 180, 277 and 285 (note the amino acids in the figure).

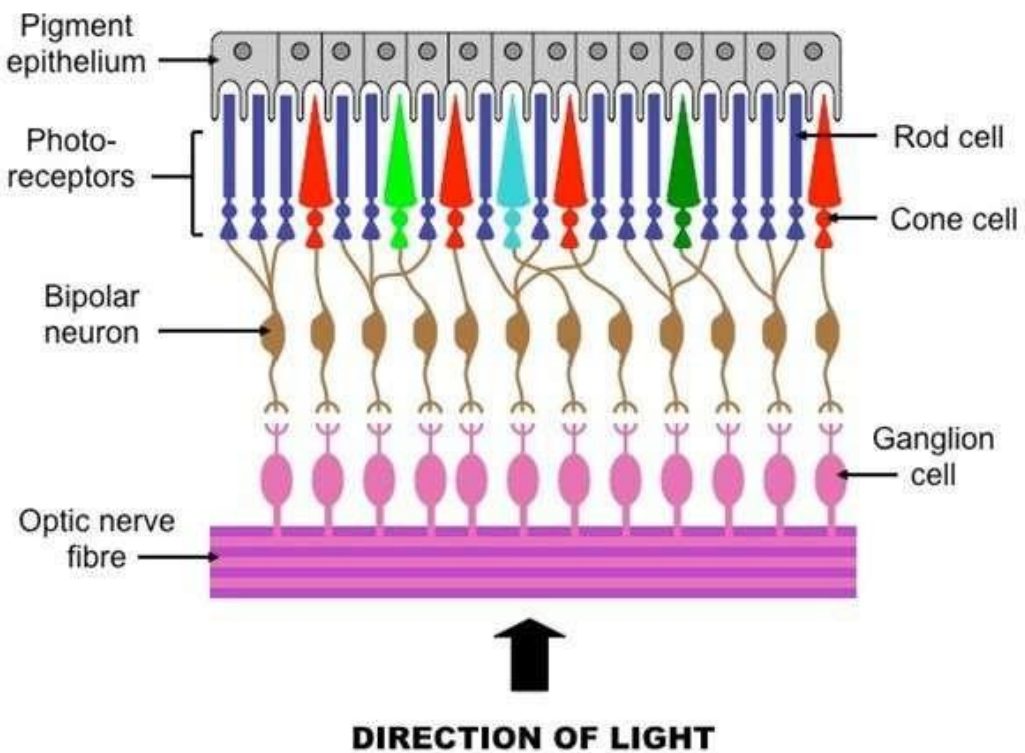
The amino acids for the red cone have **hydroxyl groups**, while the amino acids in the green are non-polar.



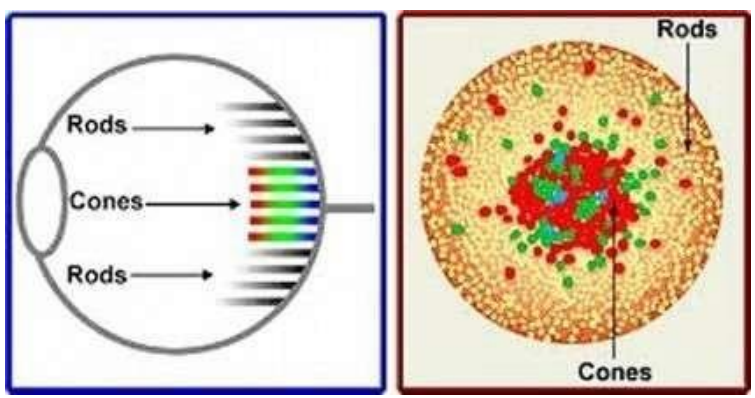
A hydroxyl group has been added to each amino acid in the red pigment causing a λ_{max} shift of about 10 nm to longer wavelengths (lower energy).

Rods vs. cones

- Location, light absorption, number, structure, photoreceptors, chromophores, image sharpness, sensitivity (amplification)

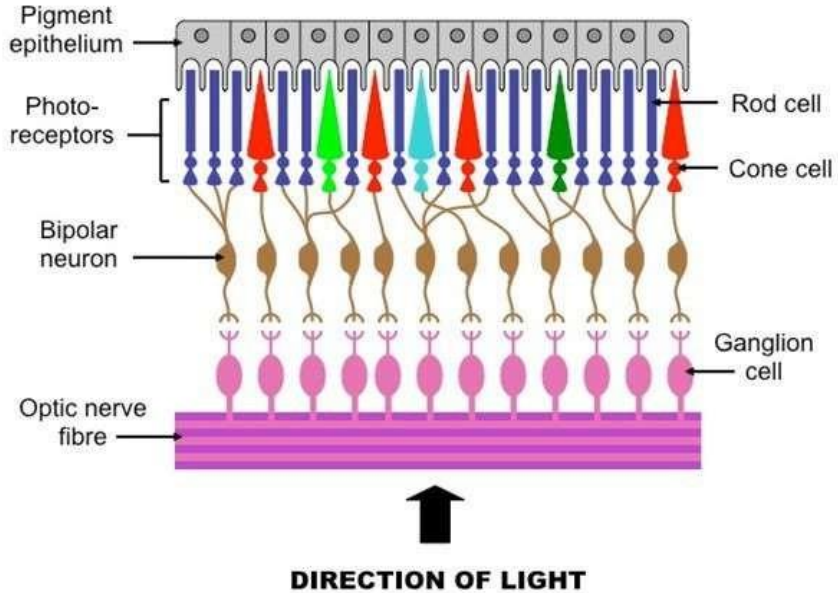


Sharpness and sensitivity of viewing images depend on the brain determining the number and location of the photoreceptor cell(s) that passes an impulse to any given nerve fiber.



Fovea

Rods vs. cones



Sharpness and Sensitivity

Sharpness and sensitivity of viewing images depend on the brain determining **the number and location** of the photoreceptor cell(s) that passes an impulse to any given fiber.

1. **Image Sharpness** :
As expected, we can see much better in bright light than in the dark. As in, the image is much sharper in bright light.

The reason why the image is not as sharp in the dark is because multiple rod cells are connected to one neuron. Therefore, when the signal reaches the brain, the brain doesn't know exactly which rod cell the image came from. So, the brain tries to form an image to the best of it's ability, but it won't be very sharp.

In the bright light, since each cone cell is connected to a neuron, the brain will know exactly where the image is coming from making it sharp.

Rods vs. cones

2.**Sensitivity:**

We see better in terms of sensitivity in dim light than in bright light.

This is because there are many more rod cells than cone cells, so they can transmit a lot of signals to the brain, making a more sensitive effect in dim light. Additionally, the molecular machinery (the molecules responsible for vision) are more in number in rod cells than in cone cells. Therefore, the signal will be amplified much more in rod cells.

Color blindness

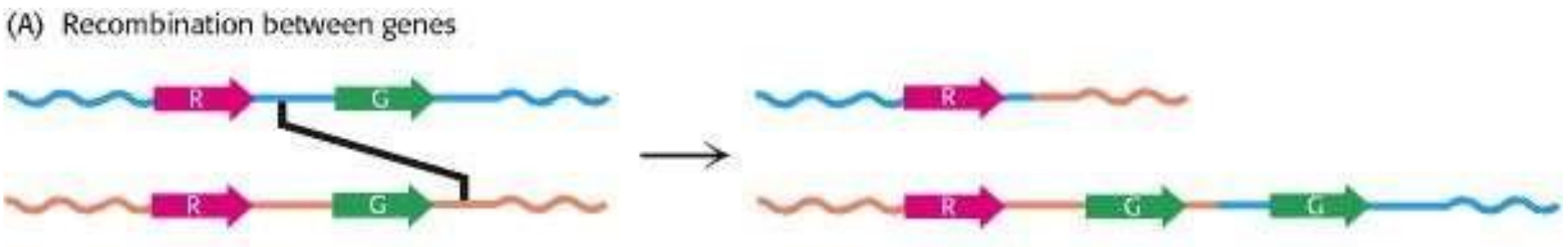
Chromosomal locations

- The "blue" opsin gene: chromosome 7
- The "red" and "green" opsin genes: X chromosome
- The X chromosome normally carries a cluster of from 2 to 9 opsin genes.
- Multiple copies of these genes are fine.

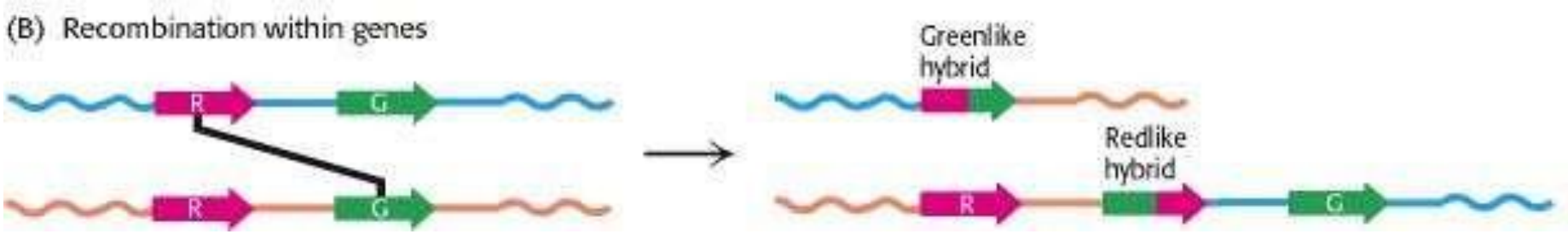
Having multiple green opsin genes
doesn't mean they'll see green "better"

Red-green homologous recombination

- Between transcribed regions of the gene (inter-genic)



- Within transcribed regions of the gene (intra-genic)



Notes from the previous slide:

- During meiosis (specifically in prophase I) – the doctor said during mitosis (metaphase) which isn't accurate, homologous chromosomes will pair up. Because the green and red genes on these chromosomes have very similar nucleotide sequences, they can exchange segments. This swapping of genetic material is called genetic recombination or crossing over.

- This process creates new combinations of genes on each chromosome. When these chromosomes are passed on to offspring, it results in genetic diversity and this explains exactly why brothers (who are not identical twins) can look different from one another.

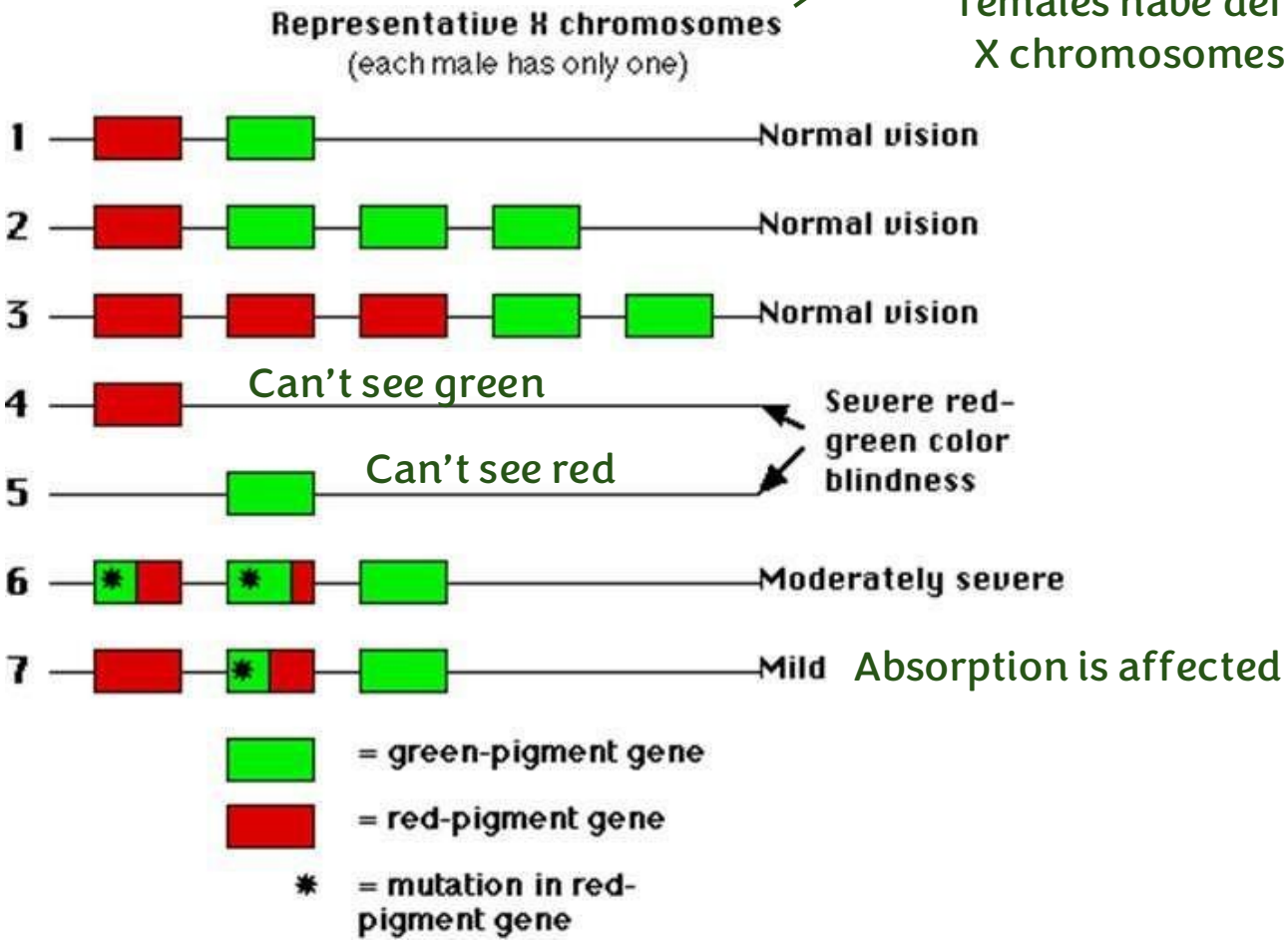
- Recombination can occur in two ways: **intra-genic** that occurs within the gene (red & green opsin genes have similarities so after recombination they form hybrid gene of green or red, or **inter-genic** that occurs between genes (part of a chromosome can be transmitted to another one without exchange).

- In intra-genic recombination, we worry about how the transmitted gene segment will affect the order of nucleotides. This is especially important in photoreceptors, where just three specific amino acids determine wavelength absorption (Any shift in these nucleotides can alter which wavelengths of light the photopigment absorbs).

- In inter-genic recombination, we worry that one chromosome may lose an entire gene responsible for detecting a particular color which might lead to color blindness, like in the previous slide a chromosome lost the green opsin & the other chromosome has two green opsins (note that people with 2 green-opsin genes won't see green color better)

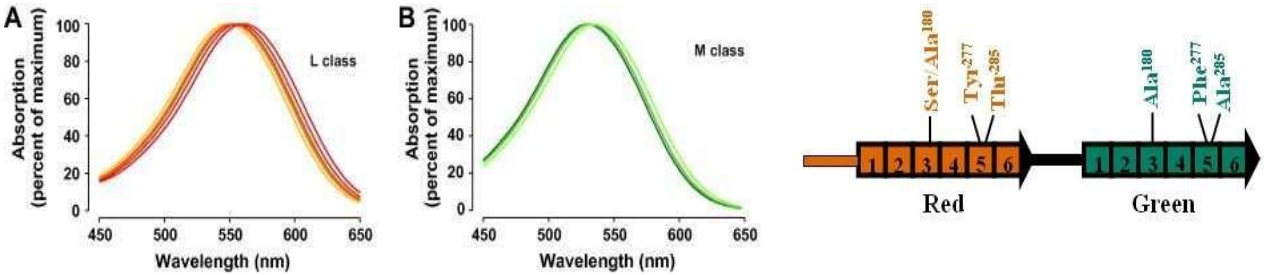
Genetic probabilities

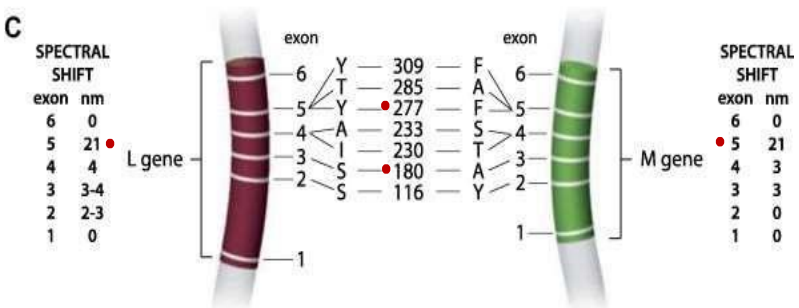
Since their genes are on X Chromosome, males are more affected, the probability that females have deficiency in both X chromosomes is usually low



Absorption is affected

Spectral fine-tuning

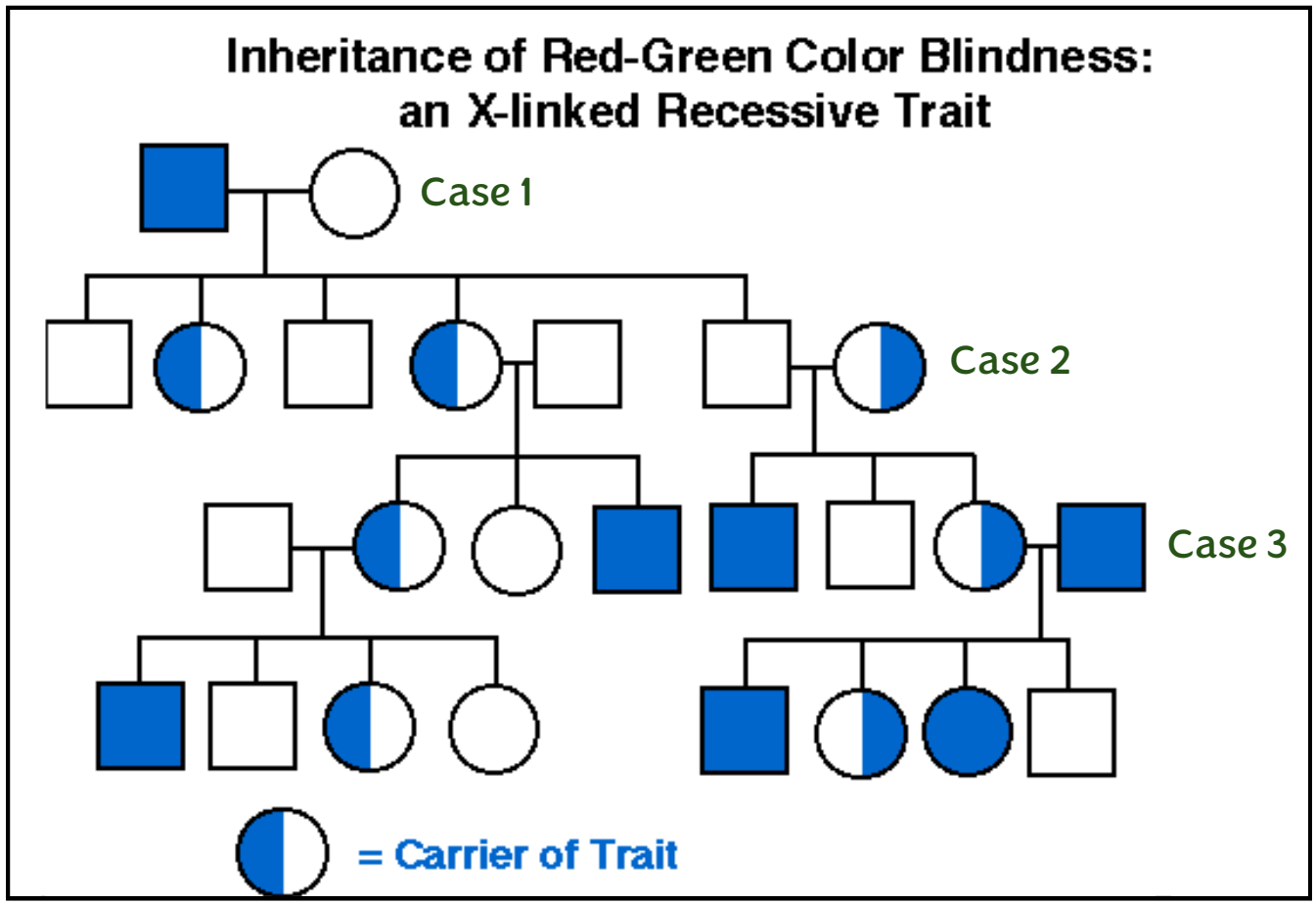




- A few important amino acids with OH groups mean that when individuals see light, what they perceive as 'red' can be slightly different between people, because genetic recombination has swapped these tuning amino acids in their opsin genes -> **Genetic polymorphism**

- The substitutions at positions 277 and 285 account for about 20 nm of the difference in peak sensitivity. Shift in peak by 20nm
- Serine (S) vs. alanine (A) at position 180 produces a considerable shift in the spectrum. Most important

Pedigree



Go to the next slide

Interpretations from the pedigree

- **Case 1:** Father has color blindness, mother does not & is not a carrier.

  - Male offspring are **not affected**, since their X chromosome comes from their mother, who does not have color blindness.
  - Female offspring become **carriers**, because they inherit their father's X chromosome (carrying the mutation) along with their mother's normal copy.

- **Case 2:** If a carrier female marries a male without color blindness:

  - Male offspring may **have color blindness** if they inherit the mutated X from their mother.
  - Female offspring are **not affected**, but may become carriers if they inherit their mother's mutated X.

- **Case 3:** If a carrier female marries a male with color blindness:

  - Male offspring: either **not affected** (if they inherit mother's normal X) or **color-blind** (if they inherit mother's mutated X).
  - Female offspring: either **color-blind** (if they inherit mother's mutated X) or **carriers** (if they inherit mother's normal X but here, all daughters will be at least carriers since the father always passes his mutated X to daughters).

Examples

Red blindness

Green blindness

People with color blindness can correctly label colors even though their subjective experience is different as their brain is trained to know what red is in a social sense.

https://www.buzzfeed.com/crystalro/red-color-vision-test

Only People Who Can See RED Really Well Can Read These Words

My own attempt;D

DOGS FIRES TOES CUTE GREET

DARK LIVE BAR LEAD COAT

BIOCHEMISTRY QUIZ LECTURE 1

External Resources

رسالة من الفريق العلمي

اللهم إن عمر عطية في ذمتك وحبل جوارك، فقِه من فتنة القبر وعذاب النار،
أنت أهل الوفاء والحق، فاغفر له وارحمه إنك أنت الغفور الرحيم.

References as cited:

1. Doctor's Lecture

For any feedback, scan the code or click on

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			