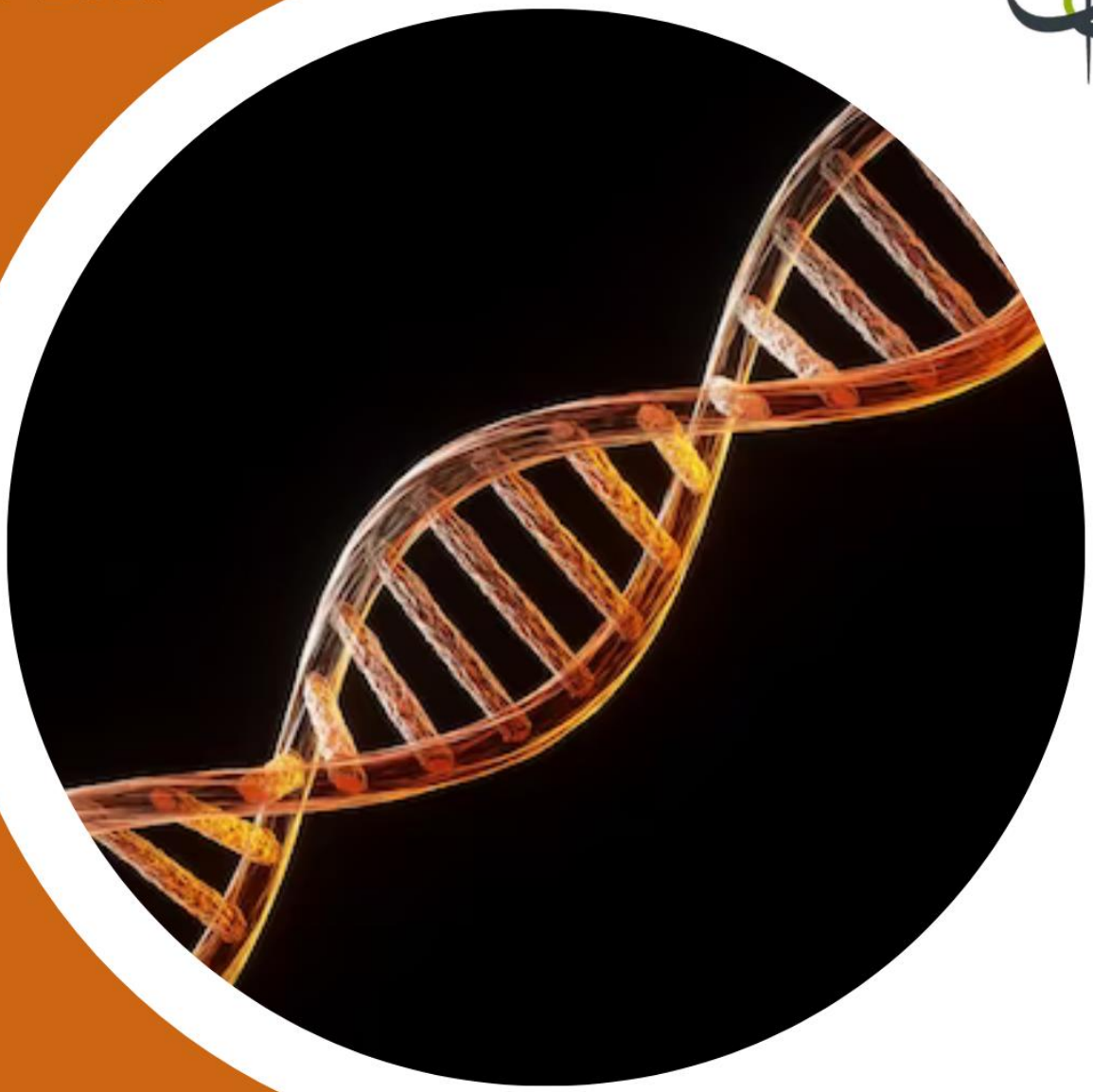
CNS

Doctor 2021



Biochemistry
Sheet (1)

Writer: Tasneem Alremawi

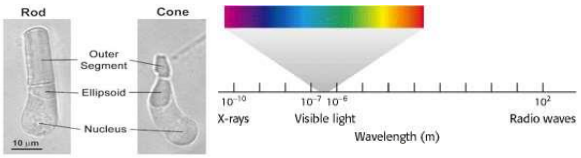
Corrector:

Doctor: Mamoun Ahram

Slides are in bold.

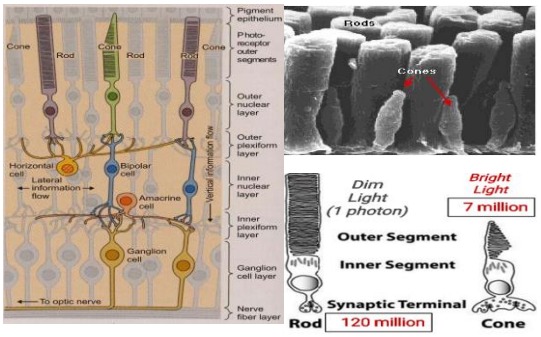
BASICS OF HUMAN VISION

There is a large spectrum of wavelengths, but we see a very small fraction of this spectrum. This is the wavelength that we can absorb which activates the signaling pathways that make us only see colors in the visible light spectrum and there are thousands of different ranges of colors within this spectrum.



There are two types of cells that are responsible for vision: Rods and Cones. They were given these names due to how they look (their shape).

They are found intermixed together in the retina and both are connected to bipolar nerves that regulate the transduction process to the brain.



- The differences between rods and cons are important, return to this table after you finish studying the sheet.

Cell Type	Rods	Cons
Shape	Thin, Tall & Cylindrical	Cone-shape
Vision Type	Responsible for vision in dim light (they can absorb as little as 1 photon, more sensitive)	Responsible for colored vision in bright light
Number	120 million	7 million
Number of types	One type with a wide wavelength range (green blue range)	Three types each with a narrow wavelength range (red, green and blue)
Distribution	All over the retina	Fovea
Connection with neurons	Multiple rod cells are connected to one neuron (blurry images)	Each cone cell is connected to one neuron (sharp images)

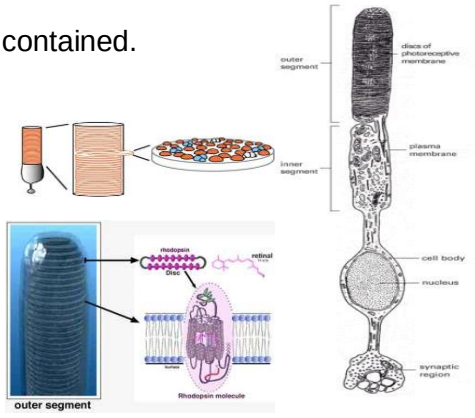
Rods Structure & Function

Structure

Rod cells consist of 4 regions:

1. **Inner Segment**: where the nucleus and other organelles are contained.
2. **Cell body**: **contains the cellular organelles** and nucleus.
3. **Synaptic region**: where the signal is transmitted to the nerves by releasing neurotransmitters (glutamate).
4. **Outer segment**: a stack of membranes "Discs" which contain signaling molecules and it's where the absorption of the light happens. It **contains the biochemical machinery needed for visual transduction.** (the most important part and we will talk more about it later in this lec)

The components of the phototransduction enzyme cascade are <u>imbedded in the membrane</u> of those ("disks").



THE DARK CURRENT

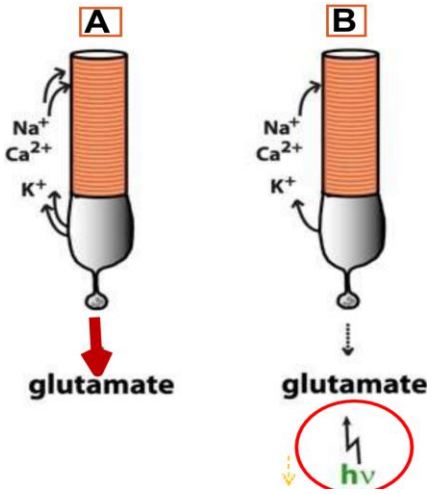
1. **Most neurons maintain a resting membrane potential (-60 to -70 mV). When excited, they open cation channels causing depolarization and opening of voltage-gated Ca $^{2+}$ channels at the synapse. Ca $^{2+}$ ions flow in and promote fusion of synaptic vesicles, which release neurotransmitters.**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

A) <u>At dark:</u>

1. **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 <u>depolarized</u>.**
4. **The neurotransmitter <u>glutamate</u> is released continuously.**

B) <u>When excited:</u>

1. **Channels in the outer segment membrane close**.
   neither Na^{+} nor Ca^{2+} get in, also Ca^{2+} gets out, which cause
2. **Rod cells to <u>hyperpolarize</u>, and**
3. **<u>Glutamate release decreases</u>** <u>which is the signal of vision.</u>

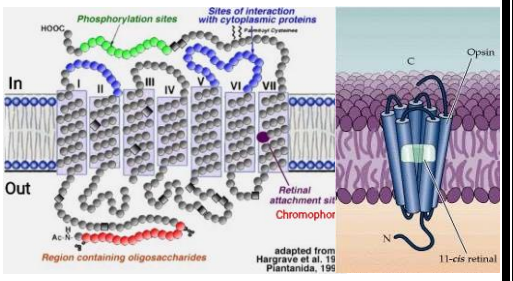


Generation of the visual signal

The players in the signal transduction:

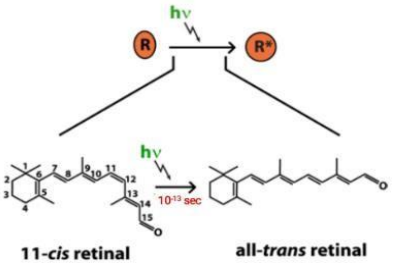
1. **Rhodopsin**: a holo-protein receptor that absorbs light formed by an apo-protein called **opsin and it have a pigment molecule** (11-cis-retinal molecule) that gets excited.
2. **Transducin.**
3. **Phosphodiesterase**.
4. **Na+ gated channels**.
5. **Regulatory proteins.**

A. RHODOPSIN: (opsin + 11-cis-retinal molecule)

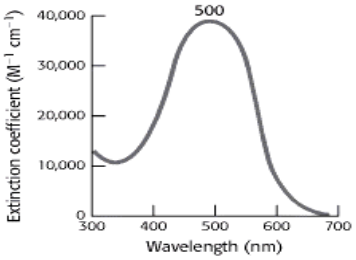


Opsin is a single polypeptide chain with 7 helical segments that span the membrane. Membrane proteins have a single transmembrane domain predominantly, followed by 7 transmembrane domain proteins which are almost always followed by G-proteins.
The last domain (number 7) contains the retinal attachment site where the chromophore gets attached.
The chromophore which known as 11-cis-retinal which is derived from vitamin A; thus, vitamin A is important for vision.
Vitamin A is derived from carotene (carrots) and that is why they say if you eat carrots, you will see better especially at night.
The chromophore converts the absorbed energy of a photon into chemical energy as a result of theconformational change in the protein structure of opsin.

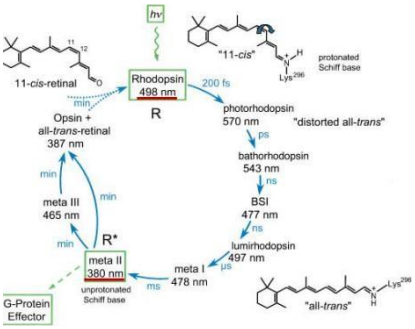
11-cis-retinal molecule (the chromophore) have trans bonds except for bond number 11 which is a cis bond (hence the name), it changes to ALL-trans when it's hit by light. This change in the structure causes rhodopsin to get activated and to also change in structure, through which transduction of the signal occurs. This change happens very fast, taking about ≈100 femtoseconds (10^{-13} secs).
(It is the fastest reaction discovered so far and the scientist who discovered it got a noble prize.)



Light absorption by rhodopsin:
When rhodopsin gets activated (by the change in 11-cis retinal's structure), it **can absorb a wide range of light** which called the visible light range (even dim light can cause a structural change). **The maximum wavelength** that can be absorbed and cause a change in structure is about **500 nanometers** (green blue range).



Rhodopsin intermediate:
When Rhodopsin is activated by light it becomes all-trans and it goes under different conformations (intermediates) and each conformation can absorb light at a different wavelength.

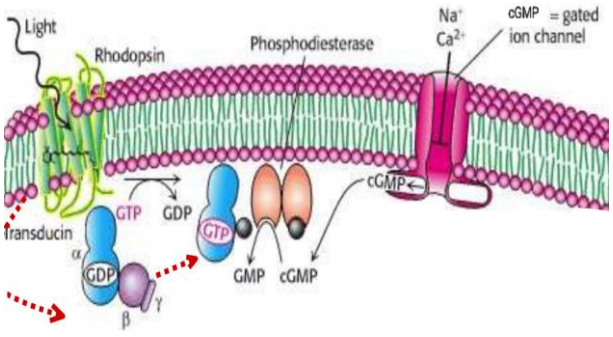


- **By itself, 11-cis retinal absorbs near UV light. But opsin changes the distribution of the electrons exciting its electrons with less energy (i.e., longer wavelength light).**
- **The chromophore converts the energy of a photon into a conformational change in protein structure.**
- **Rearrangements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

Metarhodopsin II is the activated form of rhodopsin (very important) which can transmit the signal to the G-protein transducin.

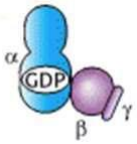
B. TRANSDUCIN → PHOSPHODIESTERASE (PDE)

When Rhodopsin is activated, **R*** (Metarhodopsin II) **binds transducin and allows the dissociation of GDP, association of GTP, and release of the α subunit.** Then, the α -GTP bound subunit interacts with cGMP phosphodiesterase (PDE) which converts cGMP inside discs in rod cells into GMP,thus reducing the amount of cGMP in the cytosol of rod cells. cGMP is important in activating Na+ gated ion channels, if the level of cGMP is high (in the absence of light) it will bind to the ion gated channels and Na+ & Ca++ will go into the cells. And when cGMP decreases (in the presence of light) it will prevent the entry of Na+ and Ca++ ions into the cells and decreases the levels of glutamate.

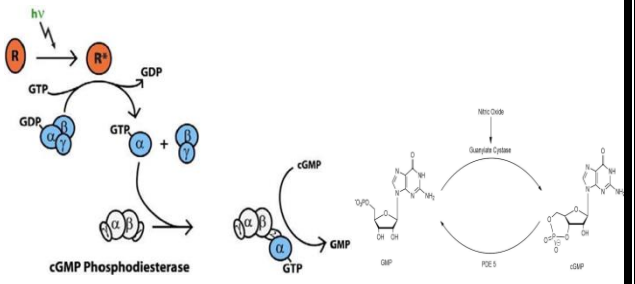


Light → reducing cGMP binding to the channels → no entry of Na+ → cell hyperpolarization and reduction in the release of glutamate → signal transduction.

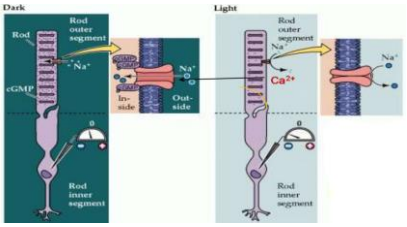
G proteins (Transducin) are heterotrimeric, consisting of α, β, and γ subunits (β and γ are inhibitory to α). **In its inactive state, transducin's α subunit has a GDP bound to it.**



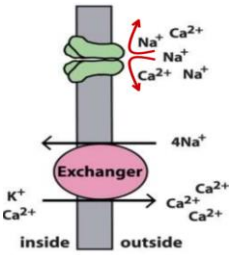
Activation of phosphodiesterase:
PDE is a heterotetramer that consists of a dimer of two catalytic subunits, α and β subunits, each with an active site inhibited by a PDE γ subunit. The activated Transducin α subunit-GTP binds to PDE γ and relieves the inhibition on acatalytic subunit, α and β subunits can then convert cGMP to GMP, reducing the level of cGMP in cells.



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

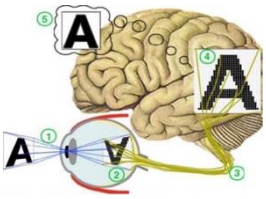


Levels of calcium ions are reduced, too:
When the channels close, Ca2+ ceases to enter, but extrusion through the exchanger continues, so intracellular [Ca2+] falls from 500nM to 50nM.
What causes this dramatic decline in intracellular [Ca2+] isn't just the closure of its channels, also the Na+-Ca2+ exchanger causes efflux of Ca2+, this drop in [Ca2+] will affect the function of the intracellular proteins.



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

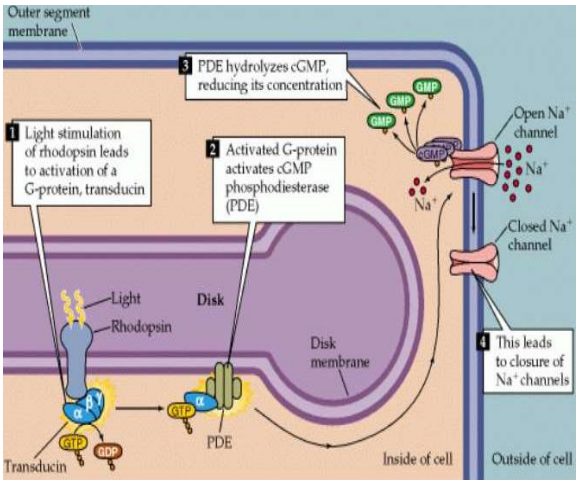
CREATING AN IMAGE



• 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.

SUMMARY OF SIGNAL TRANSDUCTION

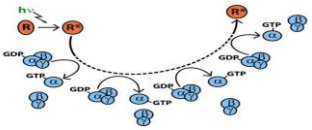
The image to the right shows one disc in the outer sigment of a rod cell, the disc's membrane contains the molecular machinery of proteins for absorbing light and activating the signaling pathway, so when the light hits, the rohdopsin changes the structure of 11-cis retinal to all-trans resulting in several intermediates of rhodopsin and the last one (metarhodopsin II) will activate the G-protein transducin then its α subunit is released and the GTP binds to it instead of the GDP, then the α-GTP bind to cGMP phosphodiesterase which converts cGMP to GMP resulting in reduction in the concentration of cGMP and ion channels will close preventing the entry of Ca2+ and Na+ and that causes hyperpolerization and reduction in the release of glutamate causing **signal transduction**.



- Rhodopsin (inactive) = opsin + 11-cis retinal.
- Metarhodopsin (active) = opsin + all-trans retinal.

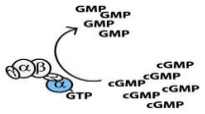
Signal amplification

1. When one Rhodopsin molecule is activated, it can activate 10 to >3000 molecules of Transducin, (The range is based on the number of photons and experimental measurements).



2. One Transducin molecule can activate one phosphodiesterase molecule (1:1 no amplification).

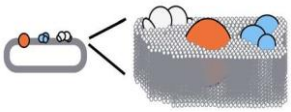
3. Then, one phosphodiesterase converts one thousand molecules of cGMP into GMP and these would affect many other cGMP gated channels (another amplification).

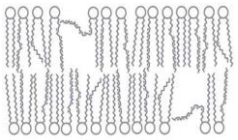


Rhodopsin (1) → Transducin (10 to >3000)
Transducin (1) → PDE (1)
PDE (1) → cGMP (1000)

FACILITATION OF TRANSDUCTION

1. **2D surface** membrane: Compartmentalization is important in speeding up reactions through placing the enzymes and substrates in a small area. Since enzymatic reactions depend on a random collision, when they are placed in a small place like lysosomes, the chance of collision is higher resulting in catalysis of reactions. The same thing happens when you place all of these components in the plasma membrane. So, instead of having enzymes and substrates finding each other in a 3D space, they move in a 2D space so they can find each other faster and that facilitates the transmission of the signal.





2. The membrane of the outer segments in rods cells is **low in cholesterol and high content of polyunsaturated, long-chain fatty acids**; meaning that the membrane is quite viscous which means that it is easy for these proteins to move through this 2D space. So, the membrane is not rigid but quite flexible, because of that **Omega 3 FA deficiency can lead to progressive retinal dystrophy.**
3. **Cooperativity of binding: The binding of one cGMP enhances additional cGMP binding and channel opening (Hill coefficient n≈3) → amplification**, so one cGMP binding makes it easier for another cGMP to bind (a characteristic of allosteric proteins), just like the heme effect. And this effect gives us a sigmoidal type of plot where we have increased successive binding/release and therefore increase in closure or opening of cGMP gated channels.So, the release of one cGMP makes it easier for the channel to close; this also works on the other way, the release of one cGMP makes it easier for the release of others and thus, easier closure of the channel.
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 easily shut down by absorption of light.**

Overall, a single photon closes about 200 channels (due to the amplification) **and thereby prevents the entry of about million Na+ ions into the rod cells.** (The molecules in this signaling machinery are highly sensitive).

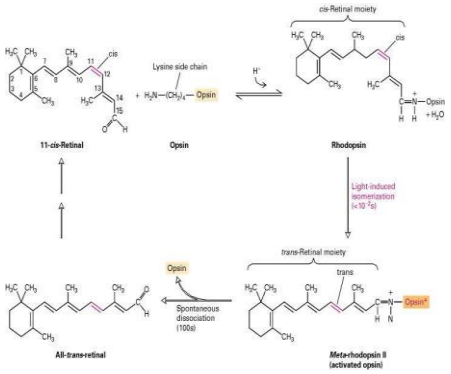
Signal Termination

Signal termination is quite important. It allows us to see the smooth movement. If the signal is not terminated or wasn't terminated fast enough, you would only see interrupted images. 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 transition between movements of the arm as it moves up or down. You would only see their final positions.

This mechanism is fast and well balanced with fine tuning, like a jewelry scale, مش ميزان خضرجي، it is precise and so sensitive to the minute changes, and the termination is done through different mechanisms which work on different levels (at the level of receptor, rhodopsin, transducin, cGMP phosphodiesterase, ion channels, guanylate cyclase and Ca2+).

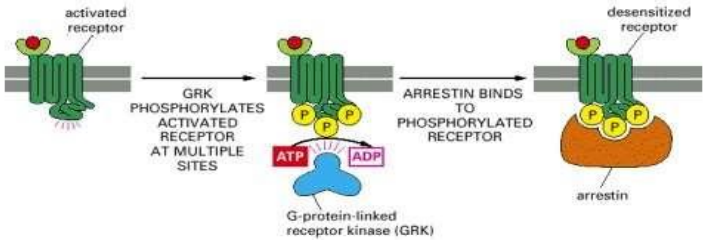
TERMINATION MECHANISMS

Mechanism I: Unstable All-Trans Rhodopsin Complex



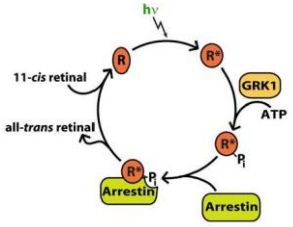
- As we know, After the 11-cis-retinal absorbs light it becomes an all-trans molecule, rhodopsin is then converted into different intermediates ending with metarhodopsin II (the active form).
- In the metarhodopsin, the interaction between the all-trans-retinal molecule and opsin is <u>unstable</u> and very week <u>resulting in the release of the all-trans molecule</u> from the opsin protein.
- Therefore, the rhodopsin molecule becomes opsin and goes back to its inactive confirmation and it cannot activate Transducin anymore.
- All-trans retinal converts back to 11-cis- retinal which can bind to another opsin to form rhodopsin once again and so on.

Mechanism II: **Arrestin Binding**
Rhodopsin kinase 1 (<u>GRK1</u>) can phosphorylate the C-terminus of active Rhodopsin (R*) or Metarhodopsin II. It does not phosphorylate the inactive form of rhodopsin.

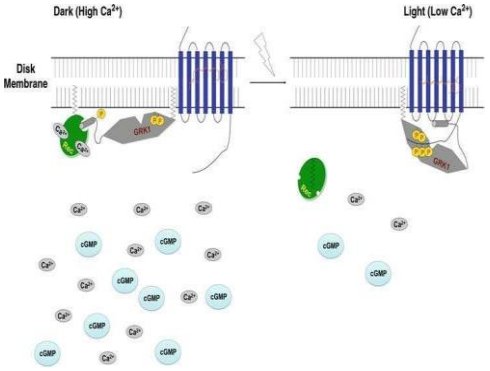


Phosphorylation of R* has the two effects:

1. **It decreases transducin activation.**
2. **It facilitates binding of the protein <u>Arrestin</u> to rhodopsin, which completely stops its activity** (preventing transducin activation even further).
   Additionally, binding of Arrestin leads to the **release of all trans-retinal** and 11- cis retinal binds instead**, regenerating rhodopsin.**



- **GRK1 is more active at low intracellular calcium ion concentration** (in the presence of light**), How?**



  - **In the dark,** the [Ca2+] is high and **Ca2+ ions bind to a protein called <u>Recoverin</u>, allowing it to anchor to the membrane, bind to GRK1** (at the N terminus helix), **and inhibit it.** (The light is absent here, so the termination isn't needed.)
  - In contrast in the light, **at low [Ca2+]** (as a part of the signal transduction mechanism) **Ca2+-free Recoverin does not bind to GRK1** and doesn't inhibit it. So, without this inhibition, the kinase is more active and can phosphorylate rhodopsin.

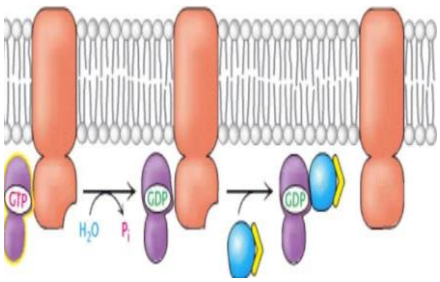
Additionally, another protein called Calmodulin (a calcium-modulated protein) is activated by the Ca^{2+} when it is present in high concentrations (at the night). **<u>Ca^{2+}-Calmodulin complex</u> (CaM) can also bind to GRK1 and inhibit it** (so calmodulin inhibits the termination of the signal since it's the function of GRK1). (We will talk about it more later on.)

- Basically: In the presence of light, the rhodopsin is activated to the metarhodopsin II, the Ca2+ conc. will become low which transduce the signal (by the low glutamate), then to terminate the signal the GRK1 will be activated by the low Ca2+ which will phosphorylate metarhodopsin II and inhibit transducin and it facilitates Arrestin binding to rhodopsin and dissociate the all-trans retinal, stopping the signal transduction.

- On the other hand, in the absence of the light, the Ca2+ conc. is high which activates two proteins (Recoverin and Calmodulin) which can bind to the kinase GRK1and inhibit it (the termination of the signal is only needed when there is light).

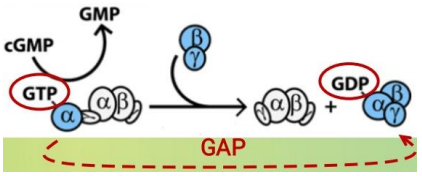
The first two termination mechanisms work at the level of chromophore and rhodopsin.

Mechanism III: **Intrinsic GTPase activity of G protein**



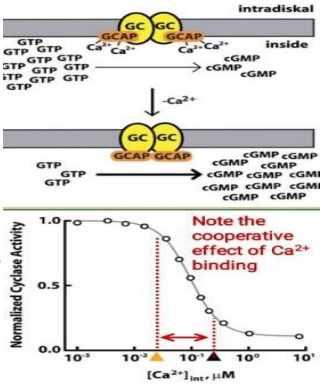
- **Transducin** (its α subunit) **has an intrinsic GTPase activity that hydrolyzes GTP to GDP** (the protein can inactivate itself; the enzyme is the substrate for itself). This GTPase activity is activated when the α subunit is bound to GTP.
- **Upon hydrolysis of GTP to GDP, transducin α subunit releases the PDE γ subunit that re-inhibits the catalytic subunit.**
- **Transducin α-GDP eventually combines with transducin βγ** inactivating Transducin and it would no longer be able to interact with the phosphodiesterase (PDE) making it inactive too and stopping the signal.

Mechanism IV: Facilitation of GTPase activity of G protein



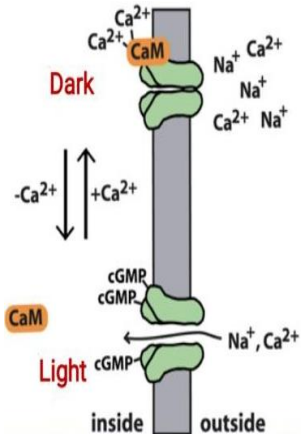
- **GTP hydrolysis** (in mechanism 3) **is slow intrinsically, but it is accelerated when it binds to the GAP (GTPase Activating Protein) complex.**
- **To ensure that Transducin does not shut off before activating PDE, Transducin and the GAP complex have a low affinity for each other** (i.e., they do not bind to each other) **until Transducin α-GTP binds PDEγ.** So, there is a period in which Transducin α-GTP is allowed to bind to the phosphodiesterase and activate it (so it can do its function) and then the GAP complex binds to the alpha subunit and activate its intrinsic GTPase activity to inhibit the process.
- **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** (the slowest step in the pathway).

Mechanism V: Guanylate Cyclase



- Guanylate cyclase is an allosteric enzyme, sigmoidal curve, it isn't turned entirely on or off by modulators, but its activity is increased or decreased by a change in the level of modulators, high levels of Ca2+ decrease guanylate cyclase activity and any reduction in the concentration of calcium ions leads to high activity of guanylate cyclase (the transition between the active and inactive form is very quick, it is very sensitive). Notice the cooperativity effect in the figure (binding of the first Ca2+ makes it easier for the others) increases the activity of the enzyme with binding of more Ca2+ ions.
- **Guanylate cyclase-activating proteins (CGAPs) are activators of guanylate cyclase.**
- **In the dark** (high levels of Ca^{2+} ions), **CGAPs bind to Ca2+ and get inhibited, so they cannot activate GCs** (Guanylate cyclases). This binding blocks their activation of guanylate cyclase making guanylate cyclase less active but not entirely inactive so it will make some cGMP that will keep the Ca2+ channels open allowing ca2+ to go in.
- In the light, **a decrease of intracellular Ca2+ ions causes them to be released from CGAPs, which can then activate guanylate cyclase** producing a huge amount of cGMP to open more channels increasing the Ca2+ intracellular concentration this inhibits the signaling pathway to allow for another reactivation (a feedback mechanism).

Mechanism VI: Ca2+-Calmodulin and cGMP-gated channels



- **In the dark**, when the calcium concentration is high and channels are open, Ca2+ binds to calmodulin to form Ca^{2+}-Calmodulin (CaM). CaM, in a sense, balances things out by keeping **some of the channels closed** to regulate the level of Ca2+ in rod cells.
- **CaM binds to the channel and reduces its affinity to cGMP**,closing the channel and keeping some control.
- **During visual transduction, the decrease in intracellular Ca2+ concentration causes CaM to be released** (Ca2+ are released from calmodulin and it becomes inactive)**. This allows the channel's affinity towards cGMP to increase, and the channel reopens in response to the slightest increase to cGMP.** (This feedback mechanism helps in the reactivation of the system.)

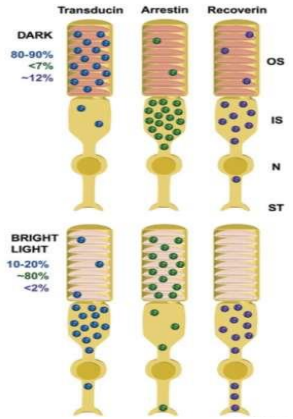
Note: Ca2+-Calmodulin (CaM) also binds to GRK1 and inhibits it.

Adaptation

You've probably noticed that if you move from a well-lit room into a dark room, you can't see anything at first. 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 or when you wake up, your eyes would be very sensitive at first, and it takes some time for you to be able to see clearly and for there to be less strain on your eyes. This is how our eyes adapt to changing light/dark conditions. This is done by rearranging the regulatory proteins (arrestin, recoverin and transducin), the localization of these proteins changes in dark vs light.

- Arrestin: inhibits rhodopsin, in the light (for termination of the signal)
- Recoverin: inhibits GRK1, in the dark. And in the light it won't active so the GRK1 will be active (for transmission of the signal)
- Transducin: activates the phosphodiesterase, in the light (for transmission of the signal).

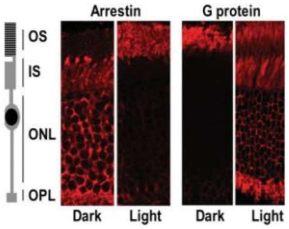
Arrestin, in the dark, stays in the inner segment of the rod cell (because there isn't any light and the rhodopsin is inactive, so it won't be close to it). On the other hand, in the light, Arresrin is localized in the outer segment (to inhibit the rhodopsin).



Transducin has the opposite behavior. In the dark, it is localized in the outer segment (transducin is waiting for rhodopsin to be activated) and in the light, it is mainly localized in the inner segment (to block the signaling pathway).

Recoverin, In the dark, is localized normally in the inner segment and some are in the outer segment. In the light, the small amount that was in the outer will go to the inner segment, by that the kinase won't be inhibited (GRK1 will be active) and it will phosphorylate the rhodopsin and it will react with the arrestin.

As we can see in the following image which is done using immunofluorescent, the proteins Arrestin and G protein (Transducin) were labelled in a rod cell for an experiment.



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

This is why adaption takes a few minutes. In the case of adapting to light, Arrestin will slowly move fromthe inner segment to the outer segment to terminate the signal and the G protein will also have to move from the outer segment to the inner segment so that the signaling in rod cells is terminated.

	Dark	Light
Arrestin	More in inner segment	More in outer segment
Transducin	More in outer segment	More in inner segment
Recoverin	More in inner segment and some are in the outer segment	All in inner segment
Result	Low inhibition, receptor ready to be activated	High inhibition, receptor ready to be inactivated

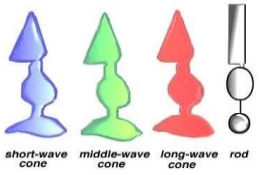
Color vision

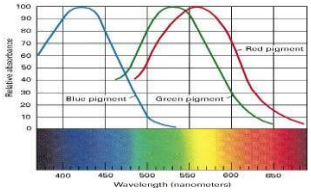
Everything we said so far was about rod cells; although the mechanism of that is similar to what happens in cone cells, it's better studied on rod cells because they're higher in number, so they are easier to study. Now we will talk more about cone cells.

CONE PHOTORECEPTOR PROTEINS

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

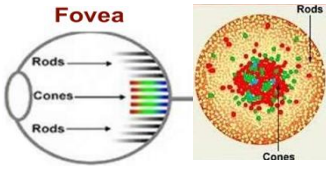
1. Short-Wave (Blue range) Cone - Responsible the shorter wavelengths and hasa peak for blue color vision.
2. Middle-Wave (Green range) Cone - Responsible for visualizing the colorgreen.
3. Long-Wave (Red range) Cone - Responsible for visualizing the color red.



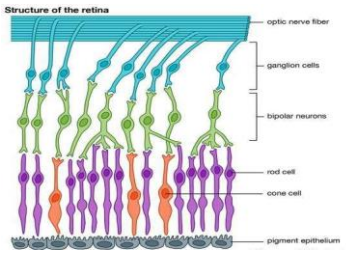


The combination of the three types of cones gives us color vision.
Notice that the range of wavelength absorption isn't as wide as rods and notice how close the activation wavelength for red and green cones are (this has implications in color blindness we will talk about it in a bit).

Rod cells are distributed all over the retina almost equally to pick any light possible from any angle, whereas cons are concentrated in a small area called **Fovea** (because in bright light, we have enough light for that small area and we don't need cone cells to be distributed all over the retina).

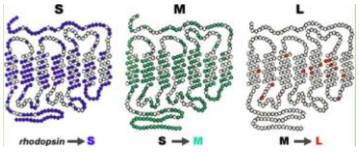


Multiple rod cells are connected to a single nerve (because the signal that they receive is very weak). On the other hand, each cone cell is connected to a single nerve, this has important implications. In the dark rod cells are active and the image resulted is fuzzy (not sharp) because the brain won't know the exact source of the signal, while in bright light we see very sharp and clear images because the brain will know the exact cone cells that are responsible for the signals.



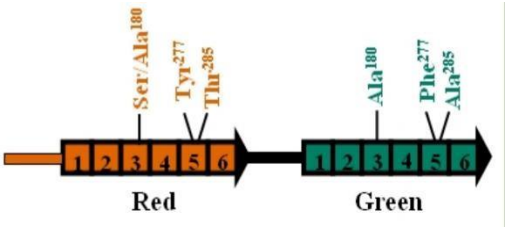
HOW DIFFERENT ARE THEY?

- **Cone opsins 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.** (So, it's actually the amino acids of the opsin protein that determine what wavelength the chromophore will absorb.)
- **Each of the cone photoreceptors vs. rhodopsin ≈ 40% identical.** In figure, the homology between rhodopsin and short-wave protein shows 40% identical amino acids. The blue color represents amino acids specific to the short-wave protein while the amino acids in white are shared between the two.



- **The blue photoreceptor vs. green and red photoreceptors = ≈ 40% identical.**
- **The green vs. red photoreceptors > 95% identical** (almost identical), that is why there is some overlap in their range of light absorption.

- There are three important amino acids that differ between the red and green photoreceptors' opsins. They are in positions 180, 277, and 285 (these different amino acids differ in their ability to absorb different wavelengths).
  - Red opsin proteins have: Ser, Tyr and Thr (all have hydroxyl groups).
  - Green opsin proteins have: Ala and Phe (all are hydrophobic).



- The amino acids for the red cone have hydroxyl groups, while the amino acids in the green are nonpolar. **A hydroxyl group has been added to each amino acid in the red pigment causing a λmax shift of about 10 nm to longer wavelengths (lower energy).**

SHARPNESS AND SENSITIVITY

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

A) Image Sharpness, 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. The brain tries to form an image to the best of its ability, but it won't be very sharp. On the other hand, since each cone cell is connected to a nerve, the brain will know exactly where the image is coming from.

B) 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:

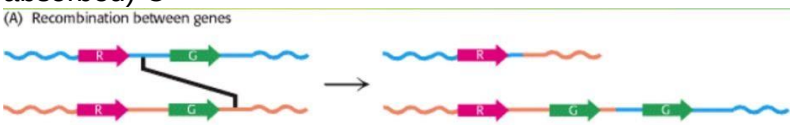
- **The blue opsin gene is located on chromosome 7.**
- **The red and green opsin genes are located on the X chromosome** indicates that any polymorphism or mutation in the red or green opsin genes makes MALES MORE AFFECTED**.**
  - **The X chromosome normally carries a cluster of 2 to 9 opsin genes.**
  - **Multiple copies of these genes are fine**, if a person has a greater number of genes, it won't make them better at seeing that color.

RED-GREEN HOMOLOGOUS RECOMBINATION

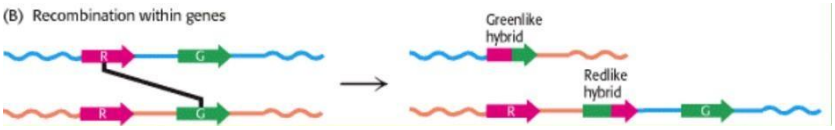
Recombination occurs in metaphase I of meiosis I, where exchange of genetic material may occur between the two homologous chromosomes (x chromosomes). The transfer of genes from one chromosome to another may be unequal with multiple recombination points from the mother's and father's chromosomes.

We said that the amino acid sequences of red and green opsins are very similar, so DNA sequence of their genes would also be similar, when chromosomes line up for meiosis they may not line up exactly the same resulting in exchange of the genetic material between the green and red genes instead of green- green or red- red. Exchange can happen in two ways:

1- **Inter-genic (recombination between transcribed regions of the gene,** in the noncoding region**)** the result would be one chromosome with red genes only without the green and the other with extra green gene, and if a person had the first chromosome (the one without the green gene) he won't be able to see the color green (the wavelength of the green won't be absorbed) ☹



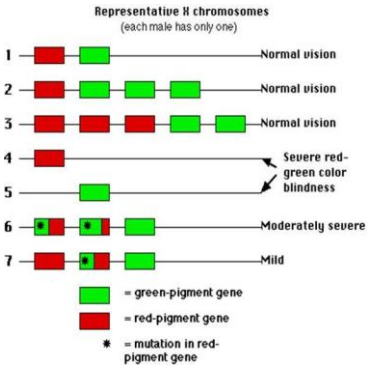
2- **Intra-genic (recombination within transcribed regions of the gene).** The individual may end up with the two chromosomes with a hybrid gene that has some of the green photoreceptor and some of the red with different degrees, in the picture below the first chromosome is missing some green and some red (his ability of seeing red and green depends on the place where the recombination happened) and the second chromosome has full red and green with additional part in between red and green (he will be able to see both green and red).



GENETIC PROBABILITIES

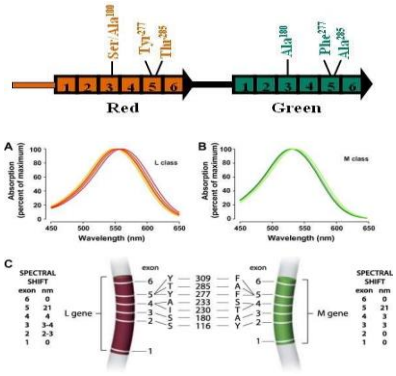
The figure to the right illustrates the different genetic probabilities. If it was for a male, then he would only have one X-chromosome, so each scenario will give the effect as written.

1. Scenarios 1-3 give normal vision as both red and green photoreceptors are present (multiple copies of the gene are fine and give no advantage).
2. If one gene (red or green) is totally missing, then that individual will have severe red-green color blindness. (more common than blue color blindness).
3. Someone with combinations of parts of red and green, with most of the red gone as in scenario 6, this could lead to moderately severe color blindness.



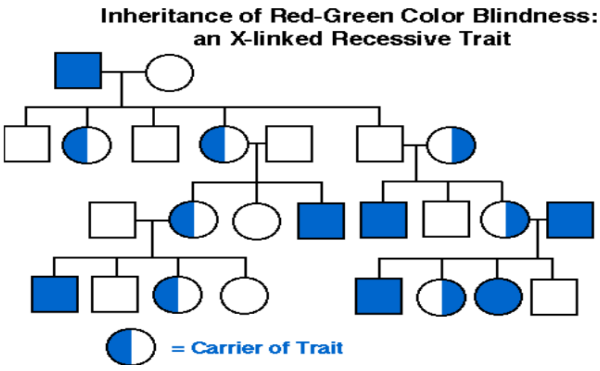
SPECTRAL TUNING

1. Individuals are not equal in how they visualize color. So, some people will see red differently than how others do. The reason is genetic differences (polymorphism) in the three amino acids that we talked about before or others as:
2. **The substitutions at positions 277 and 285** (exon 5) **account for about 20 nm of the difference in peak sensitivity** making the ability to see colors different among people. (Numbers in this example aren't for memorization.)
3. **The presence of serine vs alanine at position180 produces a measurable shift in the spectrum.**



PEDIGREES

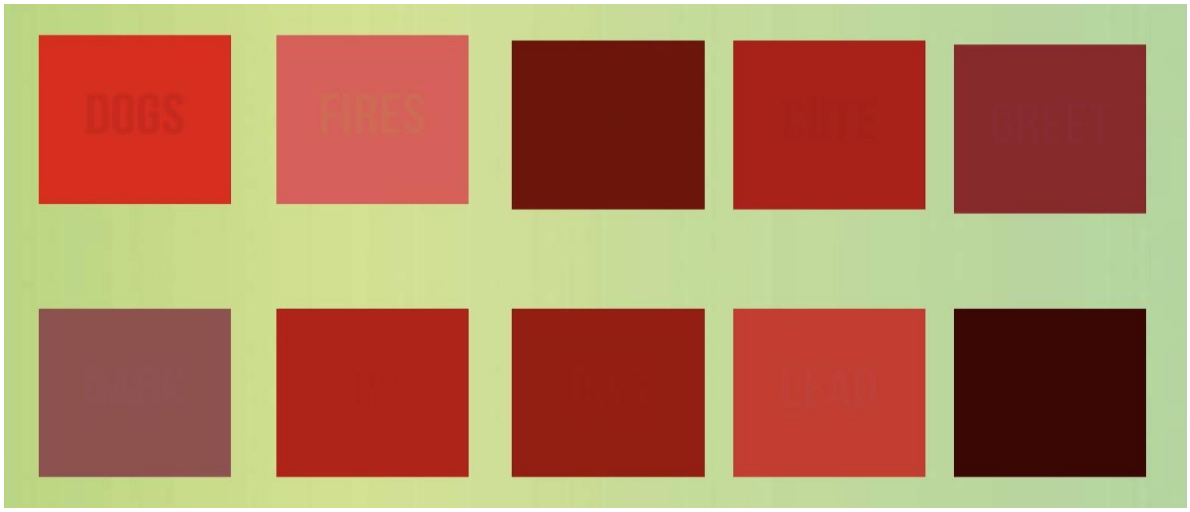
Pedigree is a family tree from a genetic perspective.



For example, this is an X-linked recessive disorder, males are more affected due to the fact that they only have one X chromosome. And only females can be carriers of the disease. In the exam the doctor may give us a pedigree and ask if it represent an x-linked disease (or green- red color blindness).

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

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



It is: dogs fires toes cute greet dark live bar lead coat.

Past papers

1- Which of the following is TRUE about arrestin:
a. Works by phosphorylation of target protein.
b. In Dark it is existed at high levels at the outer segments of photoreceptors.
c. It causes the release of all cis retinal rhodopsin.

2- All of the following are mechanisms to amplify visual signal except:
a. Each photon excites many rhodopsin.
b. Each rhodopsin excites many transducin.
c. Each transducin excites many PDE.
d. Each PDE converts many CGMP.
e. All in the same compartment.

3- When light strikes the eye there is an increase in:
a. The activity of the transducin.
b. The amount of transmitter released from the photoreceptors.
c. The concentration of all-trans retinal within the photoreceptors.
d. The concentration of calcium within the photoreceptors.
e. The activity of guanylyl cyclase.

4- Activation of transducin by light activates an enzyme which:
a. Hydrolyzes cGMP.
b. Increases the dark current.
c. Activates adenylyl cyclase.
d. Releases calcium from intracellular stores.
e. Depolarizes the membrane.

5- Visual transduction involves the following molecular feature:
a. Ca2+ ions bind to rhodopsin kinase and inhibit it.
b. Retinal plasma membrane is very fluidic easing molecular interactions.
c. Amplification involves activation of CGMP phosphodiesterase by G proteins.
d. Arrestin binding to rhodopsin activate its phosphorylation.
e. During adaptation to the dark, recoverin is mainly localized to the inner segment.

6- Which statement is WRONG about signal termination in photoreceptor cells:
Answer: Inactivation of G cyclase due to decrease intracellular [Ca2+].

7-Which one of the following is TRUE about vision:
Answer: cGMP decreases when transducin activated.

8- The function of Cones:
Answer: For color vision.

اللهم انصر أهلنا بغزة وسائر بلاد المسلمين.

Answers: 1.A 2.C 3.A 4.A 5.B

V2: The highlighted points in page 10.