Cells responsible for vision

	Rod cells	Cone cells
Shape	tall and cylinder	cone-shaped
Vision type	vision in dim light (they can absorb as little as 1 photon)	colored vision in bright light
Number	120 million	7 million
Sharpness	not sharp (multiple rod cells are connected to one neuron)	sharp image (each cone cell is connected to one nerve)
Sensitivity	more sensitive (more in number—> transmit a lot of signals to the brain and those signals will be more amplified than in cone cells)	less sensitive
	they can be divided into three sections: 1. Outer segment: contains the biochemical machinery needed for visual transduction packed into stacks of membranous vesicles ("disks"). 2. Inner segment: Consists of the cell body where the nucleus is, and other cellular organelles. 3. Synaptic terminal: Site of neurotransmitter release.	

The dark current

In the darkness: (at rest)

- Na^{+} and, to a lesser amount, Ca^{+2} enter through cGMP gated channels in the outer segment membrane.
- K+ is released through voltage-gated channels in the inner segment.

→ **Depolarization of the cell (-35 to -45 mV) → release of Glutamate in high amounts**

When excited by light:

- channels in the outer segment membrane close → Less entry of ions

→ **Hyper-polarization → decreased release of Glutamate**

Generation of vision signals

The players	
Rhodopsin (opsin + pigment molecule)	single polypeptide chain with seven helical segments that span the membrane Has a retinal attachment site where the chromophore (11-cis-retinal) gets attached
Transducin	G protein formed of three subunits (αβγ) in its inactive state Transducin α subunit has a GDP bound to it
Phosphodiesterase	heterotetramer 1α 1β and each has an active site inhibited by a γ subunit 
Na^+ gated channels	kept open by the binding of cGMP to it
Regulatory proteins	

Mechanism:

1- when Retinal absorbs light its configuration changes from cis molecule to trans this change leads to the activation of Rhodopsin (the activated form of rhodopsin is Metarhodopsin II)

2- activated rhodopsin activates Transducin by replacing its bound GDP with GTP releasing its α subunit

3- the GTP-bound alpha subunit interacts with Phosphodiesterase which converts cGMP to GMP

4- the reduced amount of cGMP will result in closure of the ion gated channels inhibiting the inflow of Na^+ and Ca^{+2}

5- hyper-polarization of the cell and decreased release of glutamate → signal transduction

Signal amplification

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

Facilitation of transduction

Through:
1- 2D surface membrane: **compartmentalization** → higher chance of collision
2- Membrane is low in cholesterol and has high content of saturated fatty acids: **higher viscosity** → easier movement
3- Cooperativity of binding

Termination

Mechanism I: Unstable All-Trans Rhodopsin Complex

- interaction of the trans-retinal molecule to rhodopsin forms an unstable complex resulting in the spontaneous release of the all-trans molecule. Rhodopsin goes back to its inactive conformation.

Mechanism II: Arrestin Binding

- GRK1 phosphorylates the c-terminus of active Rhodopsin this causes
  a. decreased ability of Rhodopsin to activate Transducin and
  b. Increases the ability of Arrestin to bind Rhodopsin which then:
     -stops its activity completely.
     -leads to the release of trans-retinal
- Calcium can regulate the function of GRK1: in the dark (high ca+2) calcium binds to Recoverin which binds to the enzyme and inhibits it.When there's light calcium levels are low Recoverin cannot bind and the kinase is more active.
- Ca^{+2} also binds to calmodulin forming a compound that binds to GRK1 and inhibits it.

Mechanism III: Intrinsic GTPase Activity of G protein

- Gα (of Transducin) has an intrinsic GTPase activity that hydrolyzes GTP to GDP. Therefore, the protein inactivates itself.
- hydrolyzing GTP to GDP leads to binding of the α subunit to β and γ subunits forming the inactive Transducin.

Mechanism IV: Facilitation of GTPase activity of G protein *It is the rate limiting step in the recovery of rod response to light*

- Through GAP (GTPase activating protein) complex which binds to α-GTP only when it is bound to PDEγ so that Transducin does not shut off before activating PDE.
- The complex then activates the intrinsic GTPase activity of the α subunit.

Mechanism V: Guanylate Cyclase

Guanylyl Cyclase converts GTP into c-GMP. Guanylate cyclase activating proteins (GCAPs) bind guanylate cyclase and enhance its activity. ca^{+2} controls the activity of those proteins.

- Dark: ↑ ca^{+2} binds (GCAPs) blocking their activity: ↓ cGMP
- Light: ↓ ca^{+2} → (GCAPs) are free of ca^{+2} → activate guanylate cyclase: ↑cGMP

Mechanism VI: Ca2+ -Calmodulin and cGMP-gated channels *-considered an amplification step as well*

- ↑ ca^{+2} binds calmodulin forming CaM → CaM binds the channel reducing its affinity to cGMP → it closes.
- ↓ ca^{+2} CaM is released → ↑ affinity to cGMP → channel reopens in response to the slightest increase to cGMP.

Regulators	
GRK1	Phosphorylates rhodopsin
Arrestin	Binds to phosphorylated rhodopsin stopping its activity

Regulators	
Recoverin	Inhibits GRK1
GAP complex	Binds (a-GTP + y-PDE) activating α subunit's intrinsic GTPase
GCAPs	Activate guanylate cyclase → ↑ cGMP
Ca^{+2}	-Activates Recoverin -Binds to GCAPs and blocks their activity -Binds to a calmodulin → 1- inhibits GRK1 2- ↓ the channels affinity to cGMP

Adaption to light/dark conditions

	Dark	Light
Arrestin	more in inner segment	more in outer segment
Transducin	more in outer segment	more in inner segment
Recoverin	more in outer segment	more in inner segment
Overall	Low inhibition, receptor ready to be activated	High inhibition, receptor ready to be inactivated

Color vision

- Short-wave (blue) cone for visualizing the color blue.
- Middle-wave (green) cone for visualizing the color green.
- Long-wave (red) cone for visualizing the color red.

The combination of the three types of cones gives us color vision
The chromophore is the same in rods and cones. What differs is the protein receptor.

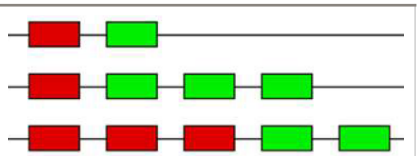
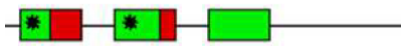
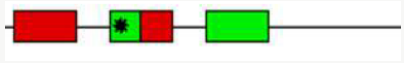
- Each of the cone photoreceptors vs. rhodopsin = ~40% identical.
- The blue photoreceptor vs. green and red photoreceptors = ~40% identical.
- The green vs. red photoreceptors > 95% identical.

Three important amino acids differ between the red and green photoreceptors. They are in positions **180, 277,** and **285.** The amino acids for the red cone have hydroxyl groups, while the amino acids in the green are non-polar. The added hydroxyl group in the red pigment causes a shift of about 10 nm in the wavelength that is absorbed.

Color blindness

Chromosomal locations: the blue opsin gene → chromosome 7
the red and green opsin genes → X–chromosome

Genetic abnormalities:

Normal vision	at least one red and one green opsin on chromosome x	
Severe color blindness	absence of either green or red opsin	
Moderately severe	1 red or green opsin and a combination of both	
Mild	both red and green opsin and a combination	

- Genetic differences (polymorphisms) result in an unequal visualization of color
- The substitutions at positions 277 and 285 account for about 20 nm of the difference in peak sensitivity.
- The presence of serine vs alanine at position 180 produces a measurable shift in the spectrum.

Majd Anaya