Biochemical pathways regulating the Function of Sensory Organs

Dr. Nesrin Mwafi
Biochemistry & Molecular Biology Department
Faculty of Medicine, Mutah University

Sensory Organs and Sensory Neurons

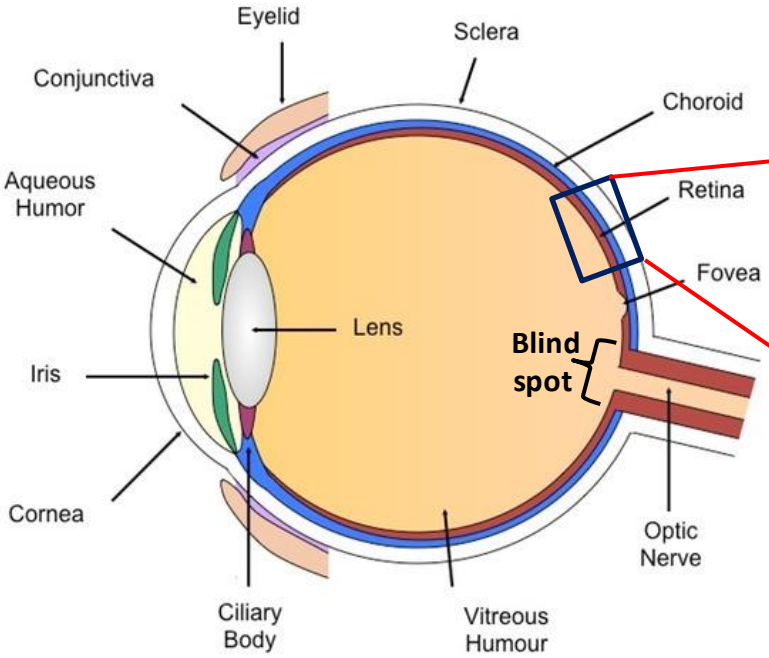
Vision >

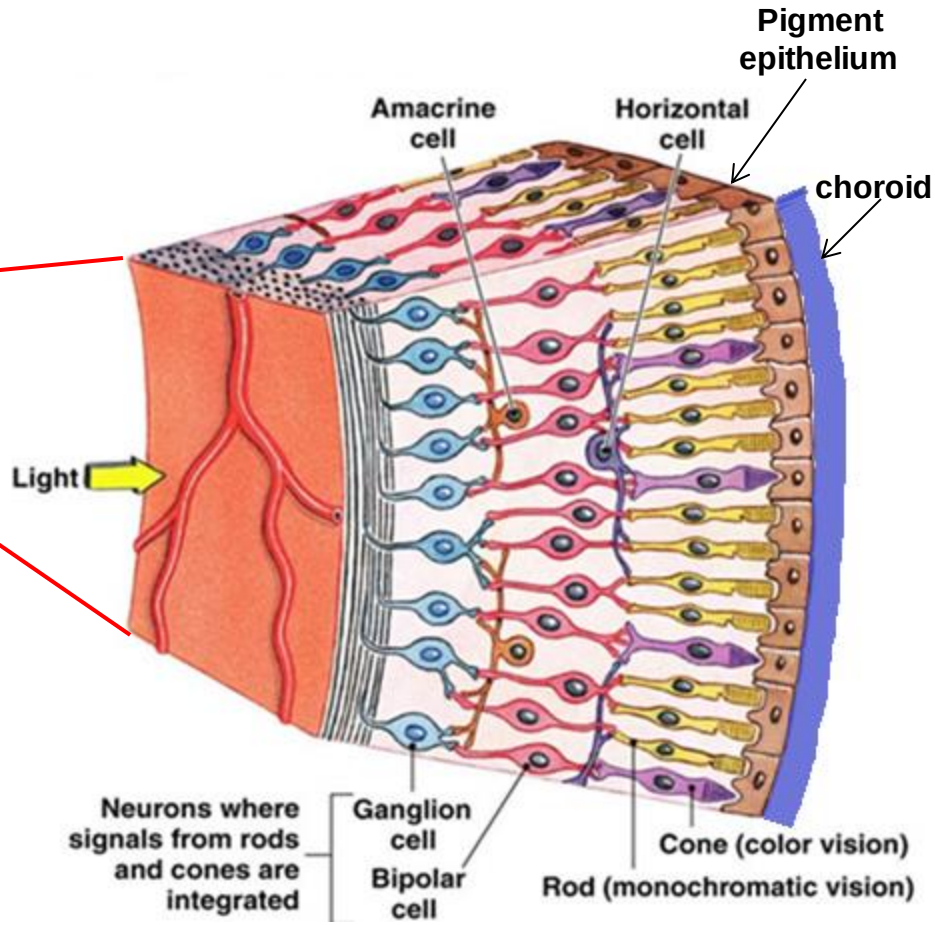
Olfaction >

Taste >

Biochemistry of Vision

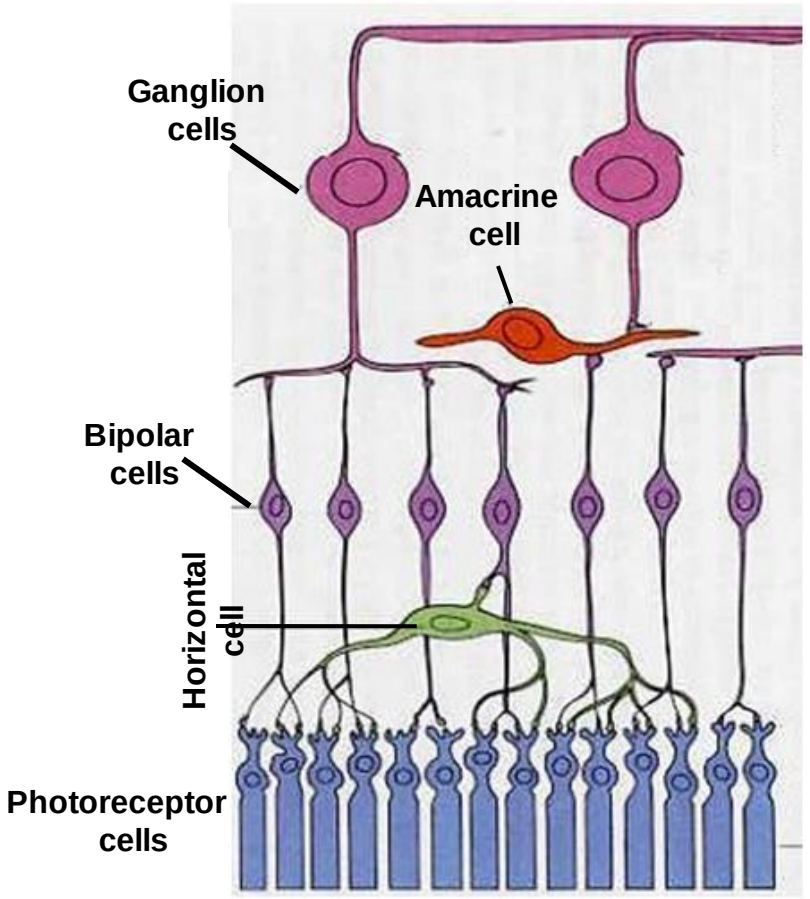
The Structure of Human Eye





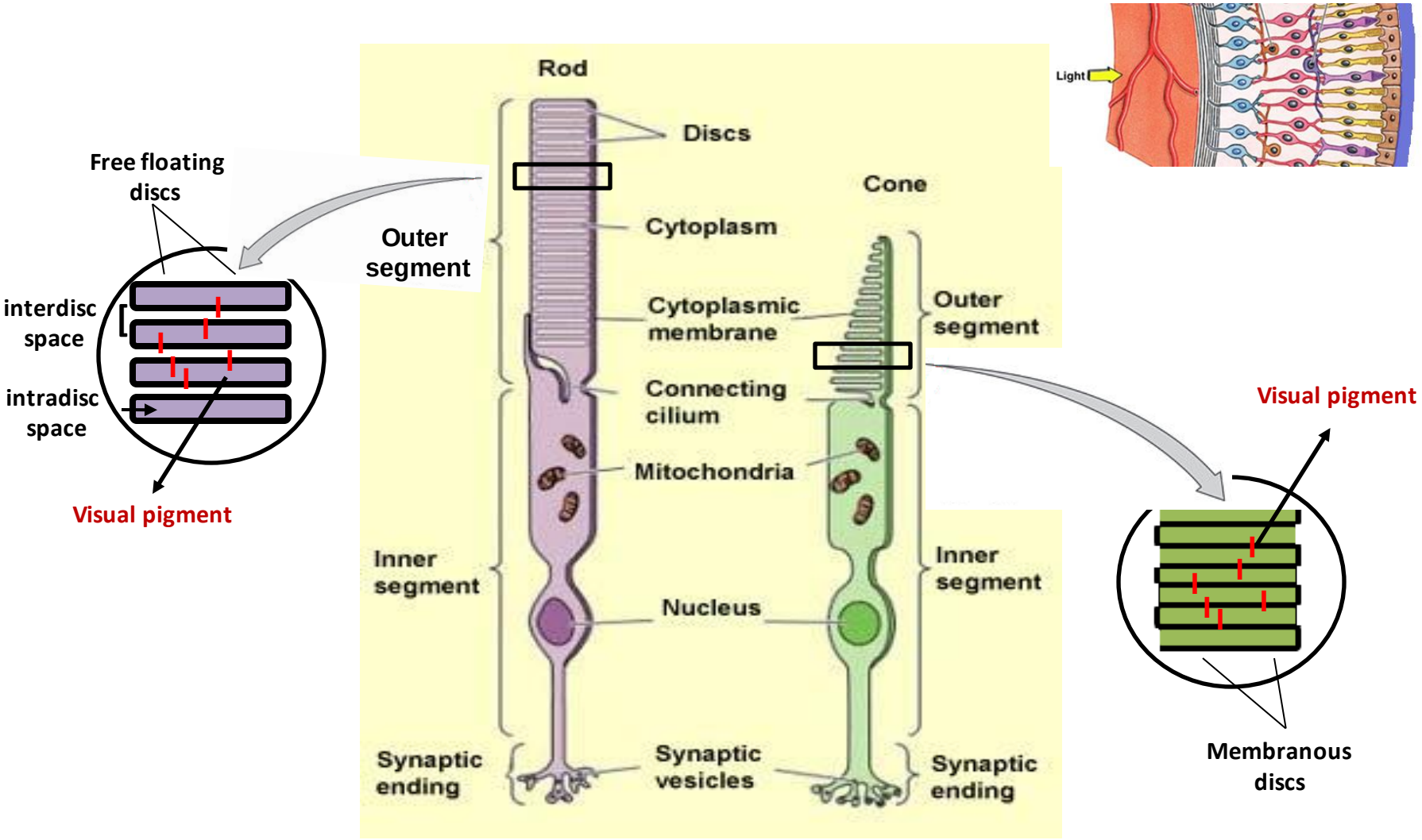
The Structure of Retina

- The retina has **3 layers of neurons** (the photoreceptor, the bipolar and the ganglion cells) and **2 layers of synapses** including the unique ribbon synapses or lateral connection via the horizontal and amacrine cells
- Horizontal cells make synapses with rods, cones and bipolar cells whereas the amacrine cells connect bipolar with ganglion cells. **Thus horizontal and amacrine cells are involved in the indirect path of visual input transmission.**

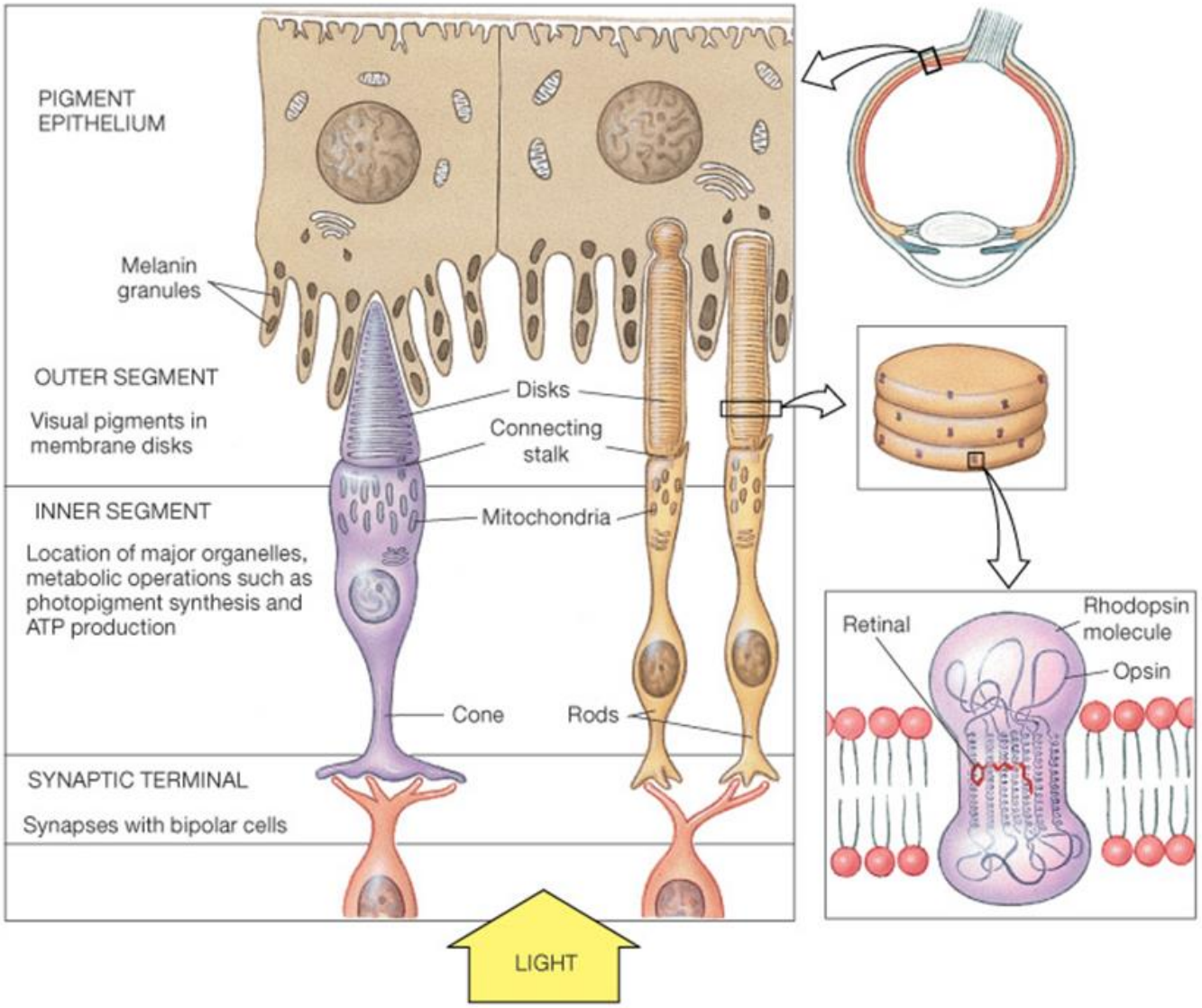


Photoreceptor cells

Retina contains two types of photoreceptors:

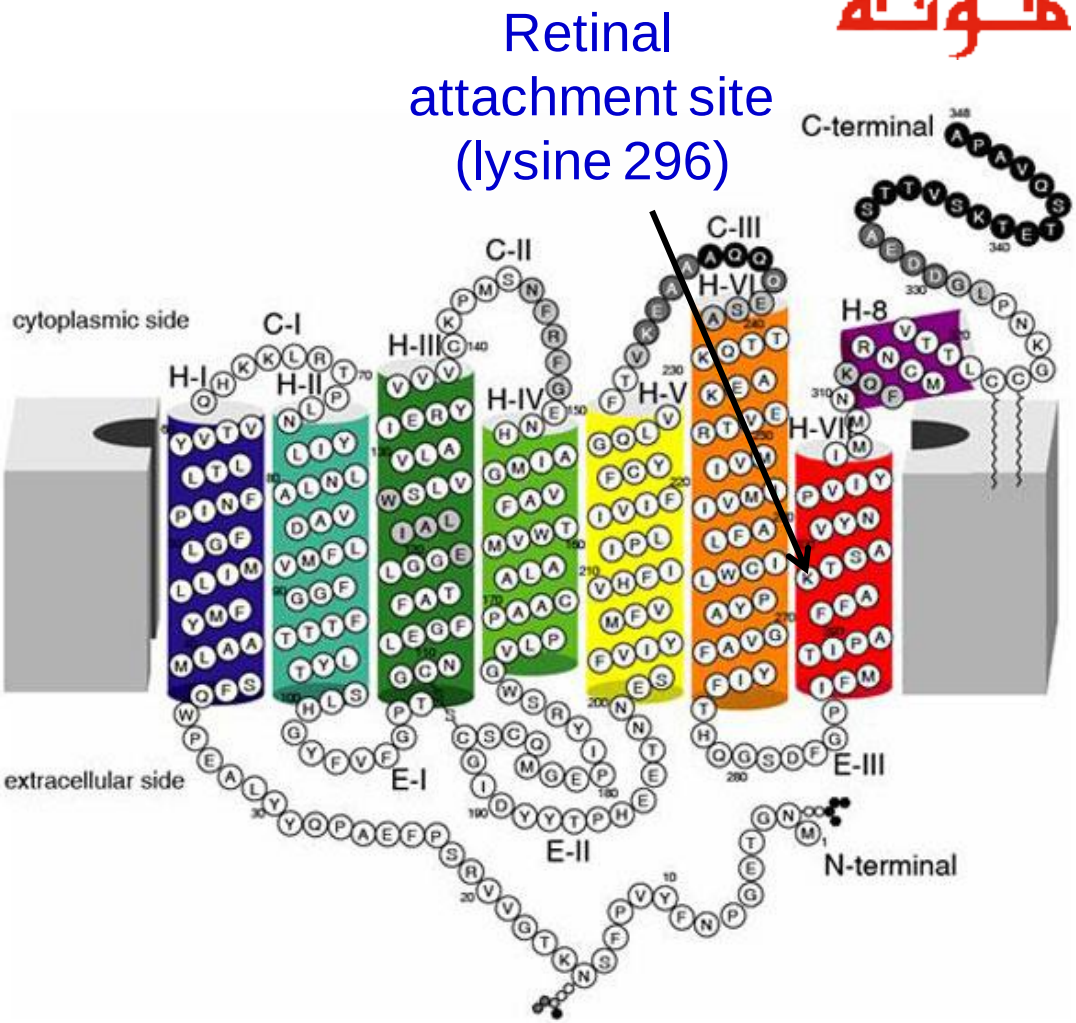


Visual Pigment

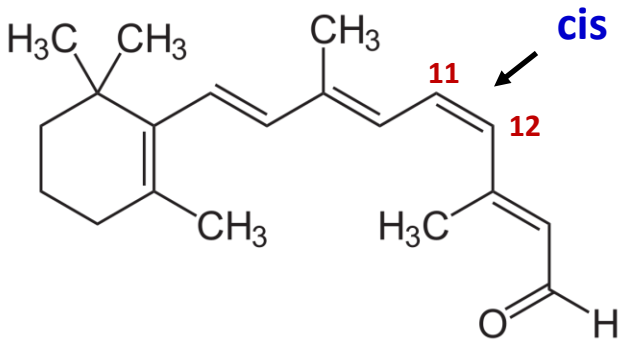


Structure of Rhodopsin

- Rhodopsin is the only visual pigment in rods
- It consists of the transmembrane protein (GPCR) called **opsin** and light sensitive moiety called **retinal** (the aldehyde form of Vitamin A)

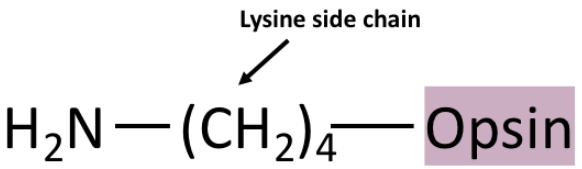


Retinal Binding to Opsin

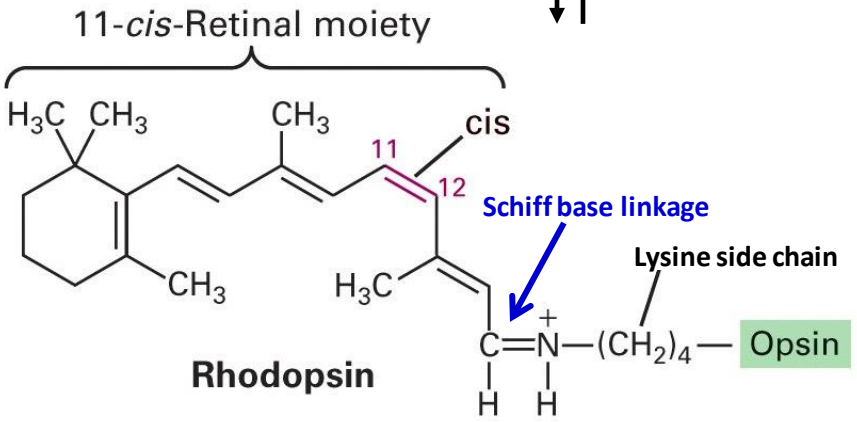


11-cis Retinal

+



Opsin



Rhodopsin

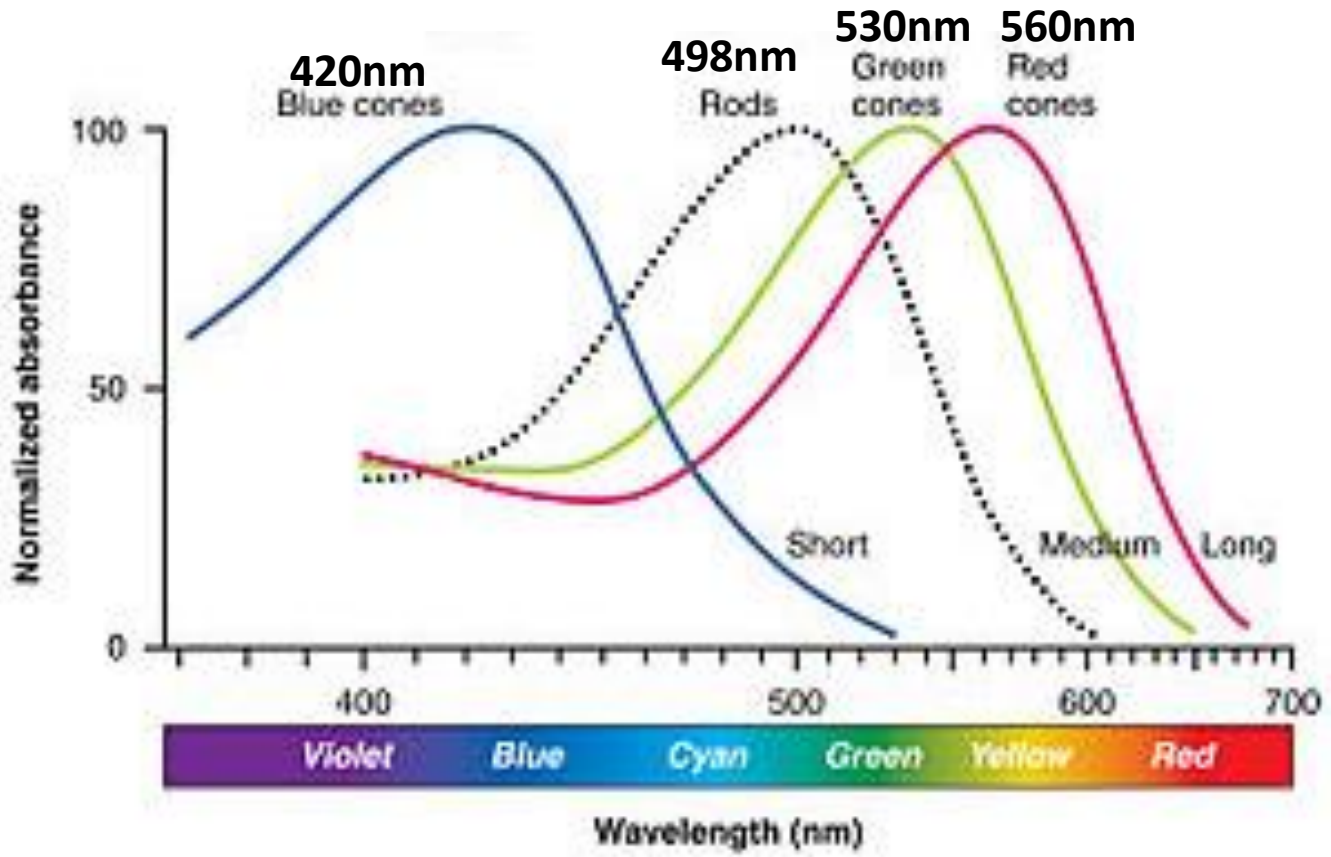
+ H_2O

Iodopsin

- Iodopsin is the visual pigment in cones consisting of cone opsin protein (photopsin) and the same light sensitive moiety: retinal
- 3 different types of iodopsins and consequently 3 different types of cone cells (which give us color vision):

1. L cones (photopsin I + retinal) → red light, 560nm
2. M cones (photopsin II + retinal) → green light, 530nm
3. S cones (photopsin III + retinal) → blue light, 420nm

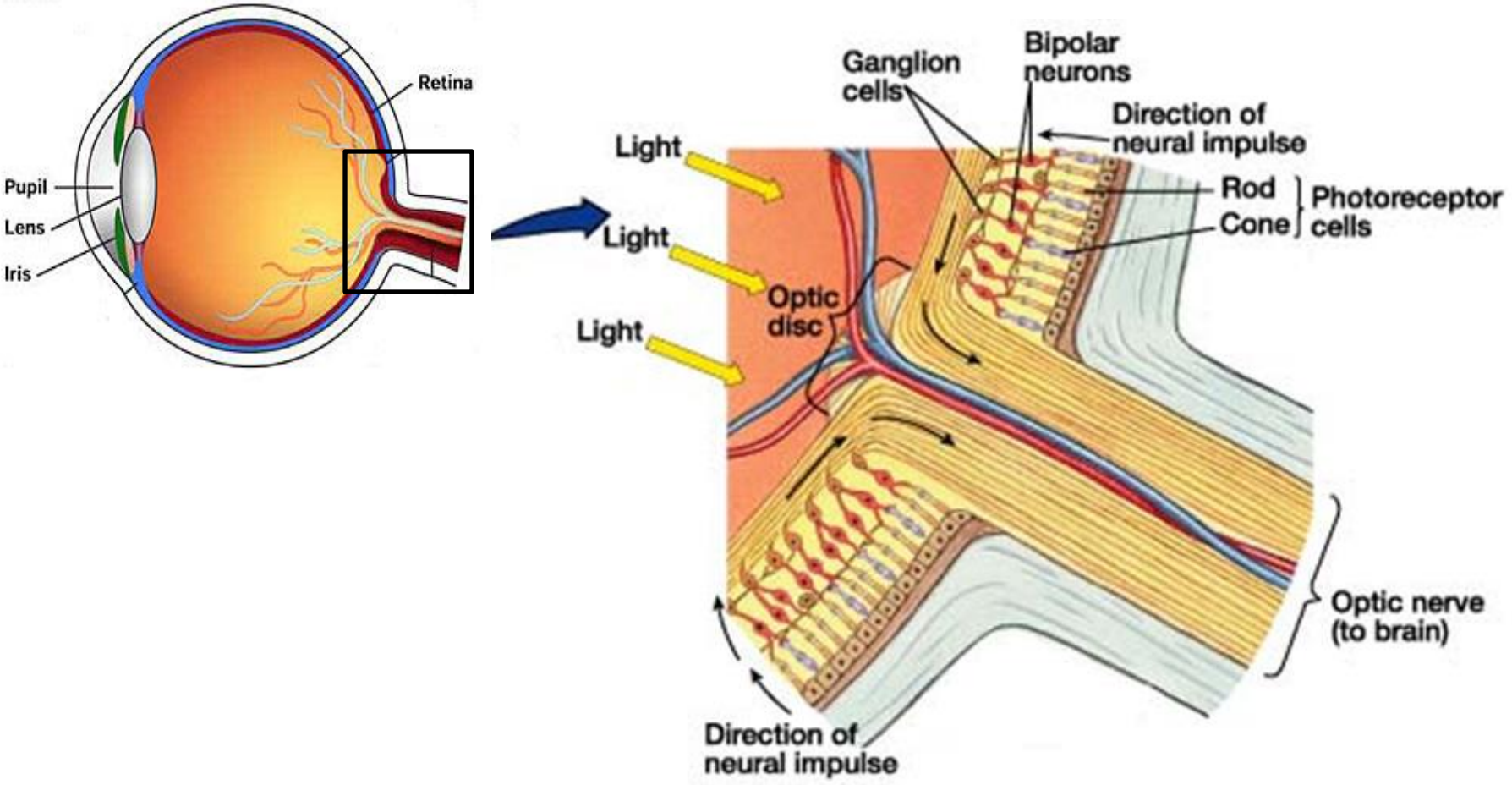
3 Different Cones



Phototransduction

- Phototransduction is the process by which the light detected by photoreceptor cells in the retina is converted into electrical (or cellular) signals.

Phototransduction



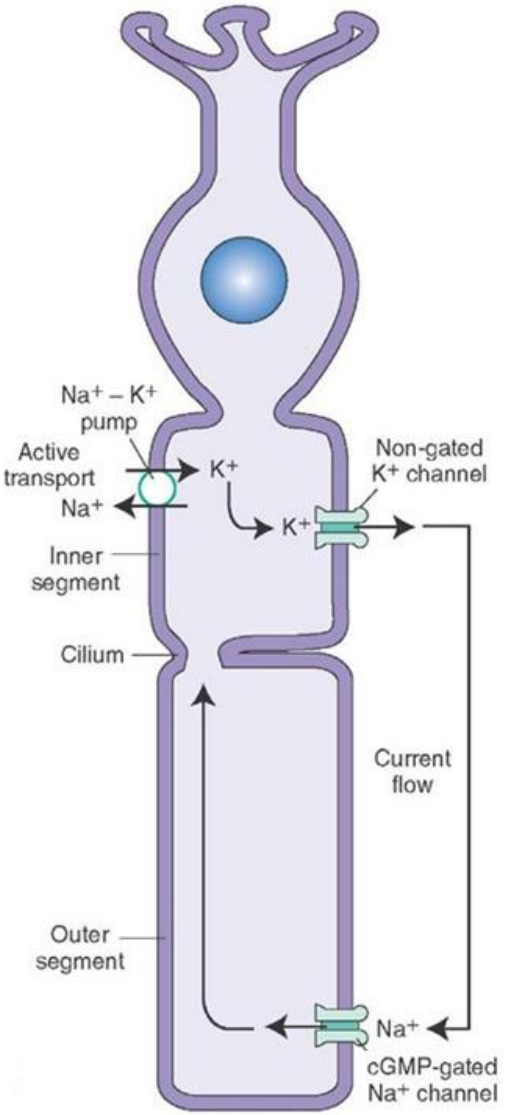
Phototransduction

- Phototransduction is the process by which the light detected by photoreceptor cells in the retina is converted into electrical (or cellular) signals.
- These are transmitted as nerve impulses back through layers of retina to optic nerve fibers
- The optic nerve carries the information to the brain to be processed there
- What is the molecular mechanism involved in visual cycle and how does the absorbed light create a response ?

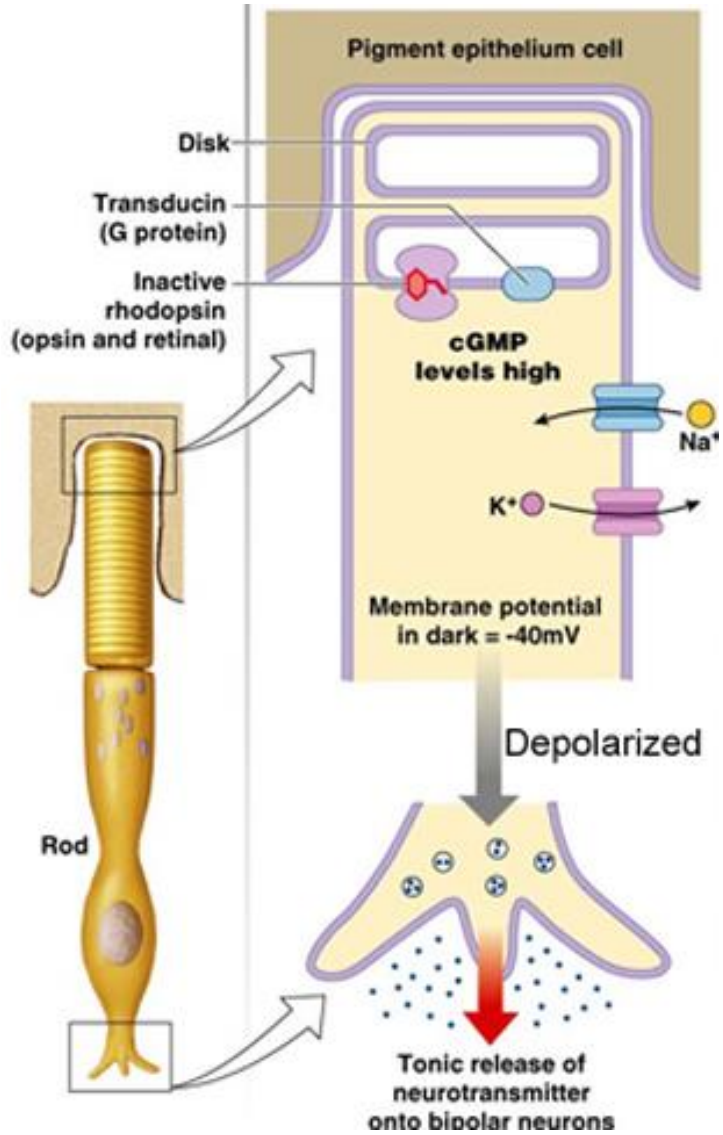
Phototransduction Cascade

- In the absence of light, the photoreceptor cell is in the depolarized state with membrane potential of -40 mV. This depends on:

1. **Non-gated K^+ channel:** outflux of **K^+** (ongoing outward K^+ current)
3. **cGMP-gated Na^+ channel:** influx of **Na^+** (inward Na^+ current known as **dark current**)
3. **Na^+- K^+ pump:** it is an active transport requires ATP (to transfer 3 **Na^+** out and 2 **K^+** in)

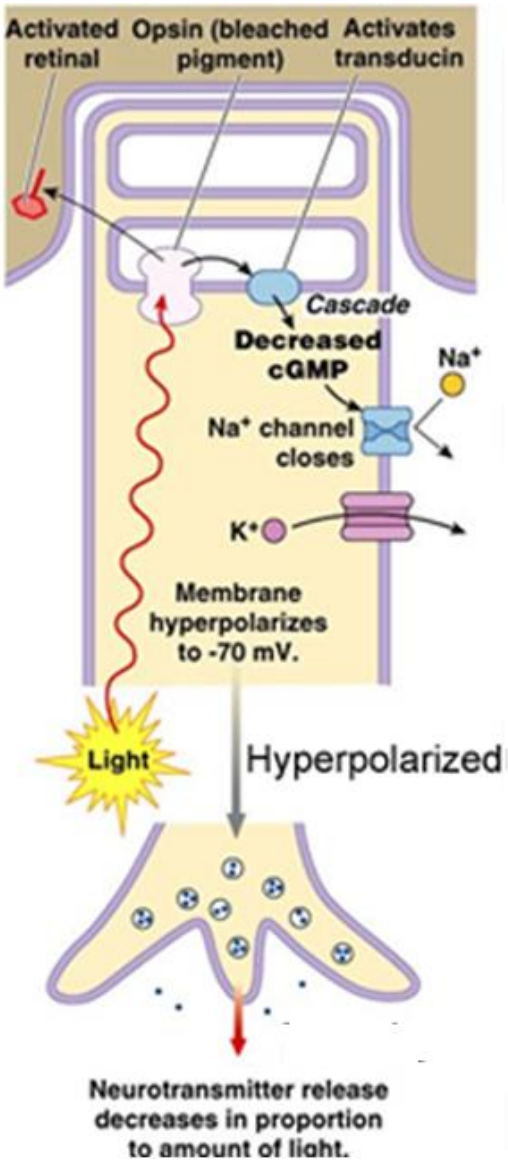


Phototransduction Cascade



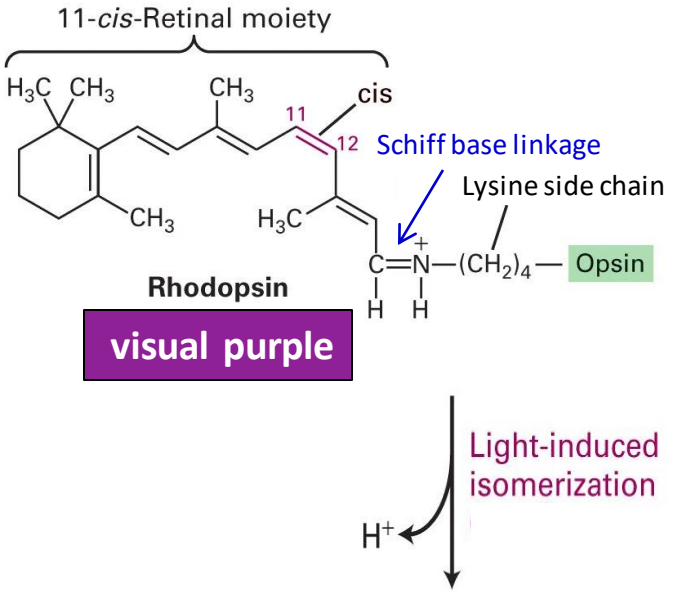
- In darkness, **rhodopsin is inactive** and cGMP level is high thus Na^+ channels are open.
- The neurotransmitter molecules are released from synaptic terminal of photoreceptor cell.

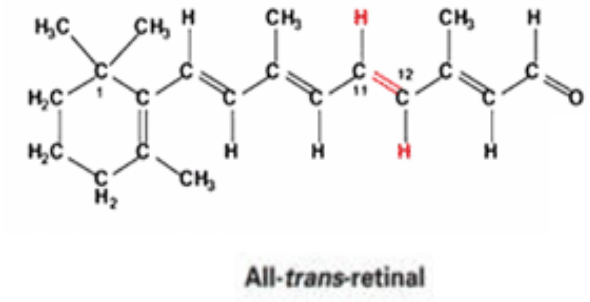
Phototransduction Cascade

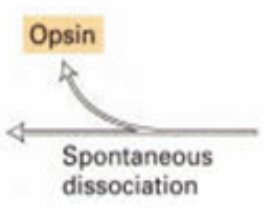


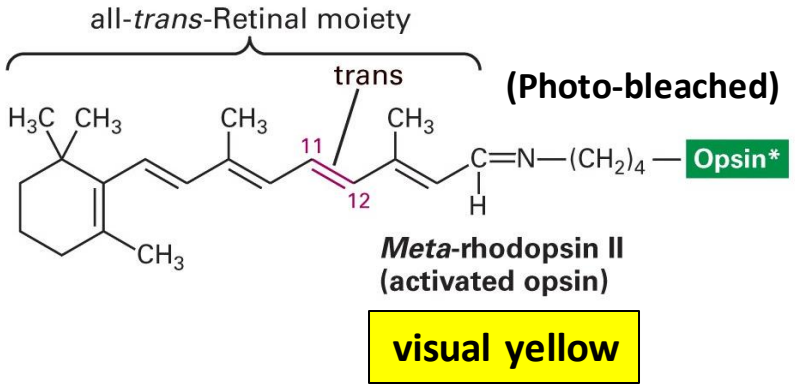
In presence of light, a series of changes occur within **rhodopsin** which activate a downstream signaling cascade resulting in the **closure of Na^+ channels**. Indeed, rhodopsin dissociates, the activated opsin decreases **cGMP** which in turn closes Na^+ channels and **hyperpolarizes** the cell. Consequently, less neurotransmitter molecules are released.

Photoisomerization of retinal

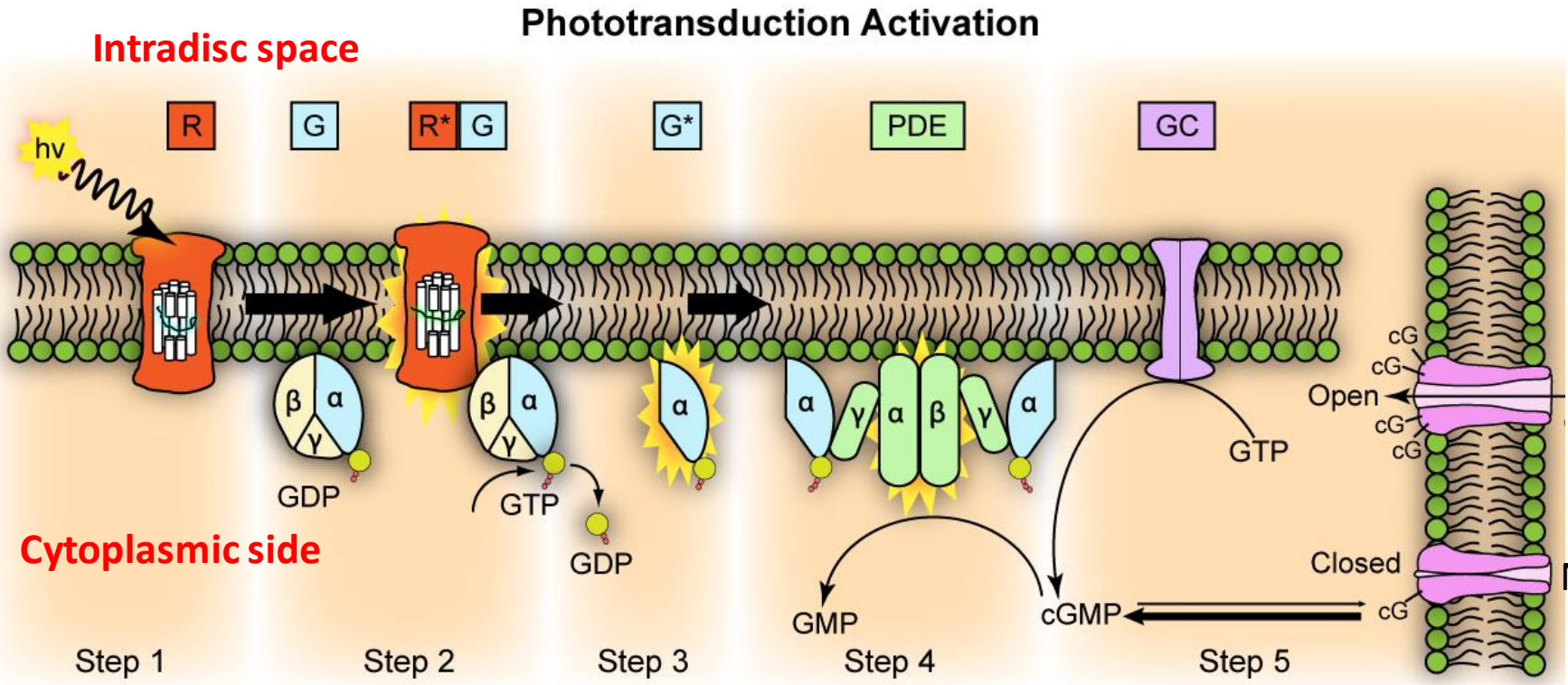








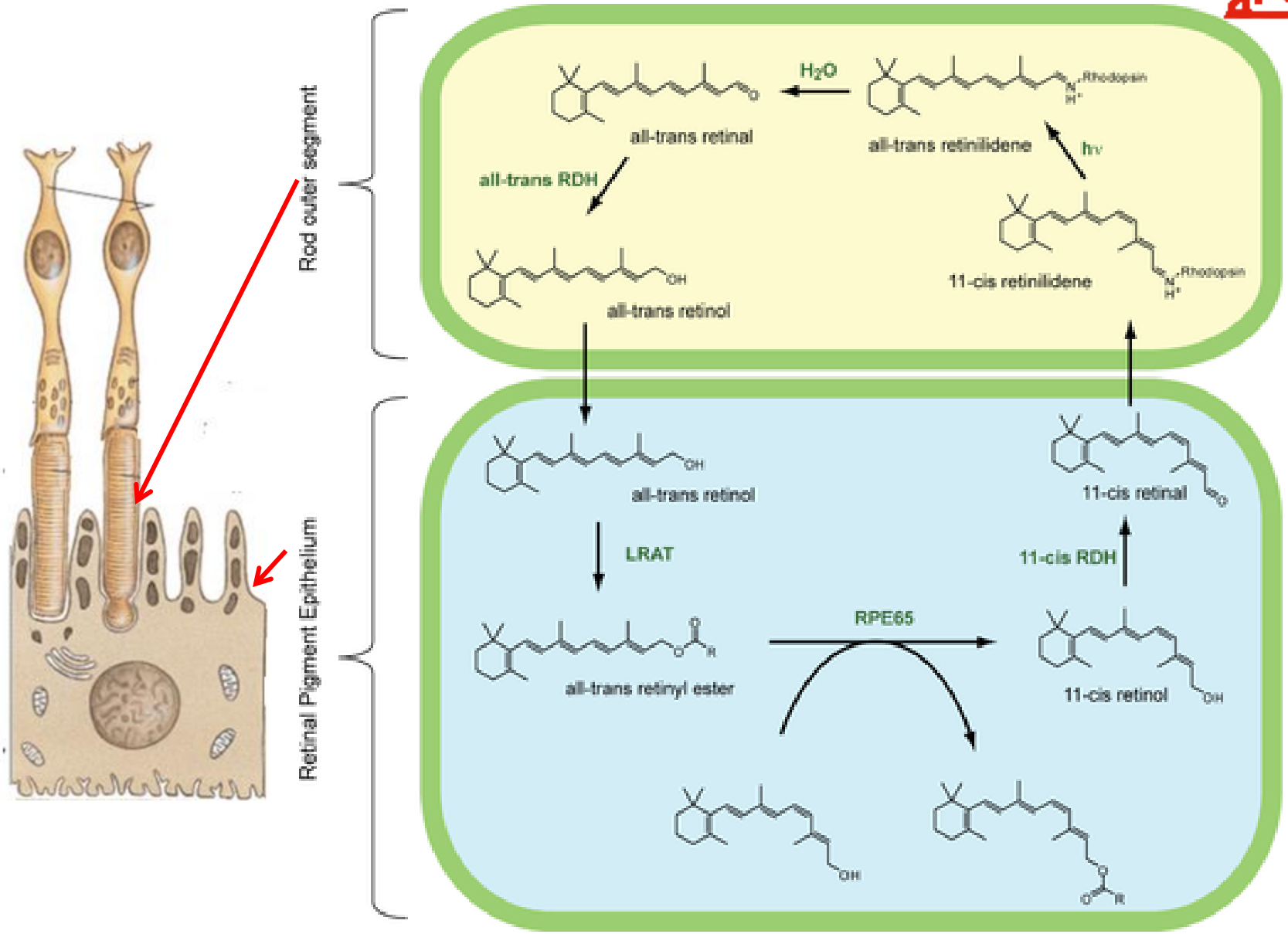
G-protein signaling pathway



G-protein signaling pathway

- The activated rhodopsin (**R***) binds to and activates the heterotrimeric G-protein "transducin" by exchanging its GDP with GTP
- The α-subunit of transducin bound to GTP (the activated transducin, **G***) dissociates from its β and γ subunits
- **G*** binds to the inhibitory γ subunits of phosphodiesterase enzyme (PDE) activating its two catalytic subunits: α and β. The activated PDE converts cGMP to GMP so reduces the cGMP level and consequently the closure of **Na^+ channels**. Thus, the membrane is hyperpolarized and the rate of neurotransmitters release is reduced
- Normally, Guanylyl cyclase (GC) enzyme synthesizes cGMP from GTP. **So cGMP is the second messenger in phototransduction cascade**

Regeneration of Visual Pigment



Regeneration of Visual Pigment

- In darkness, inactive rhodopsin consists of opsin covalently linked to 11-cis retinal via schiff base bond. Light induces photoisomerization of 11-cis retinal to all trans retinal. The rhodopsin becomes activated (called meta-rhodopsin II) and loses its visible purple color (photobleached)
- **Long after visual cycle is complete, the activated rhodopsin dissociates and the all-trans retinal is released to be recycled back to 11-cis retinal**
- **A series of biochemical reactions occur both in the outer segment of photoreceptor cell and the pigment epithelium layer in retina to regenerate the visual pigment again**
- First, all-trans retinal is reduced to all-trans retinol via all-trans retinol dehydrogenase (all-trans RDH) which travels back to retinal pigment epithelium (RPE).

Regeneration of Visual Pigment

- In RPE, all-trans retinol is first esterified by lecithin retinol acyltransferase (LRAT) to form all-trans retinyl ester (a chemically stable storage form of vitamin A in RPE).
- When further chromophore is required, the isomerase enzyme RPE65 (retinal pigment epithelium specific 65-KDa protein) synthesizes 11-cis retinol by using all-trans retinyl ester as substrate.
- 11-cis retinol is converted via 11-cis retinol dehydrogenase (11-cis RDH) to 11-cis retinal before travelling back to the outer segment of photoreceptor cell where it is again conjugated to an opsin to form new functional visual pigment (e.g. rhodopsin)

Light and Dark Adaptation

- Visual adaptation: is the ability of visual system to automatically adjust its sensitivity to accommodate a change in light intensity. ***Two types:***
  1. Dark adaptation: is the slow recovery of visual sensitivity (20-30 min) after exposure to a bright/strong light (i.e. when you move from the light to the dark).
  2. Light adaptation: is the adaptation to increased level of illumination (i.e. when you move from the dark to the light, 5 min).
- Mechanisms underlying light /dark adaptation:
  1. Pupil size to adjust amount of light reaching the retina
  2. Switch-over between rods and cones
  3. Bleaching / regeneration of photopigments

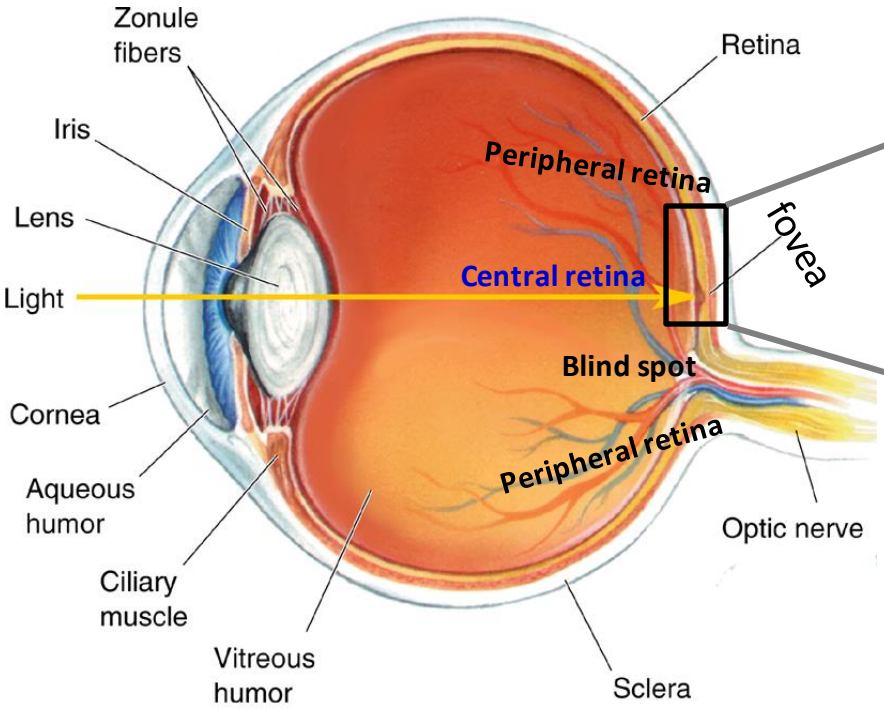
Photoreceptor cells

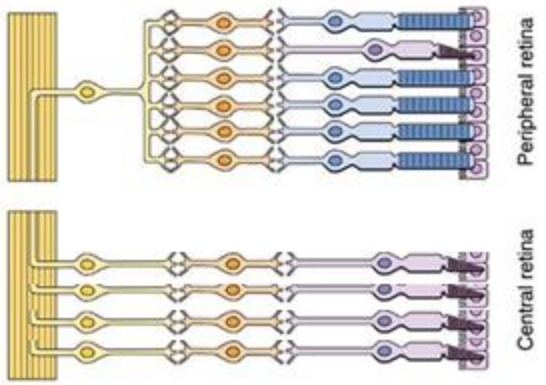
Retina contains two types of photoreceptors:

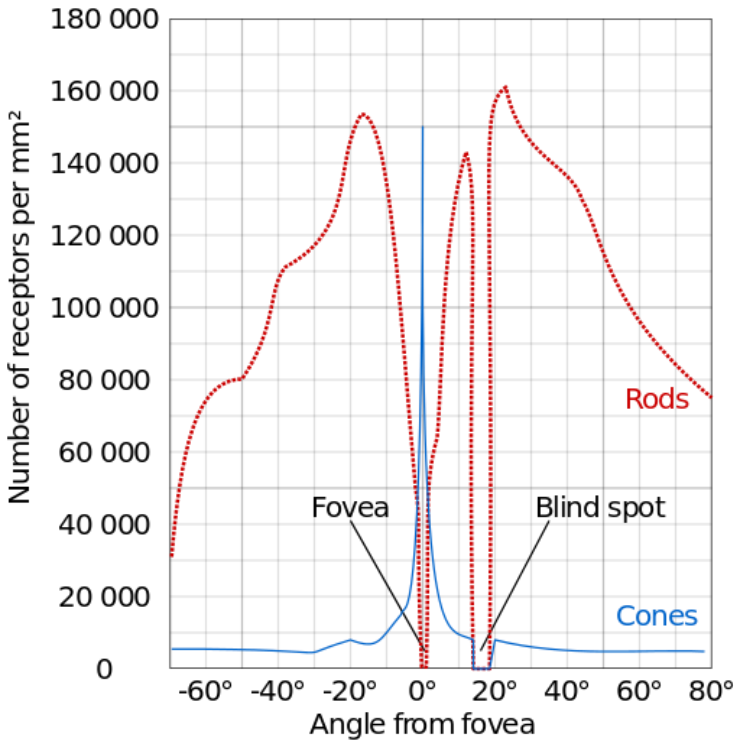
1. Rod cells: about 120 million, function in dim light (night vision) and do not perceive color, with high sensitivity and low resolution

2. Cone cells: about 6 million, function in bright light (daytime vision)and are responsible for color vision, with low sensitivity and high resolution

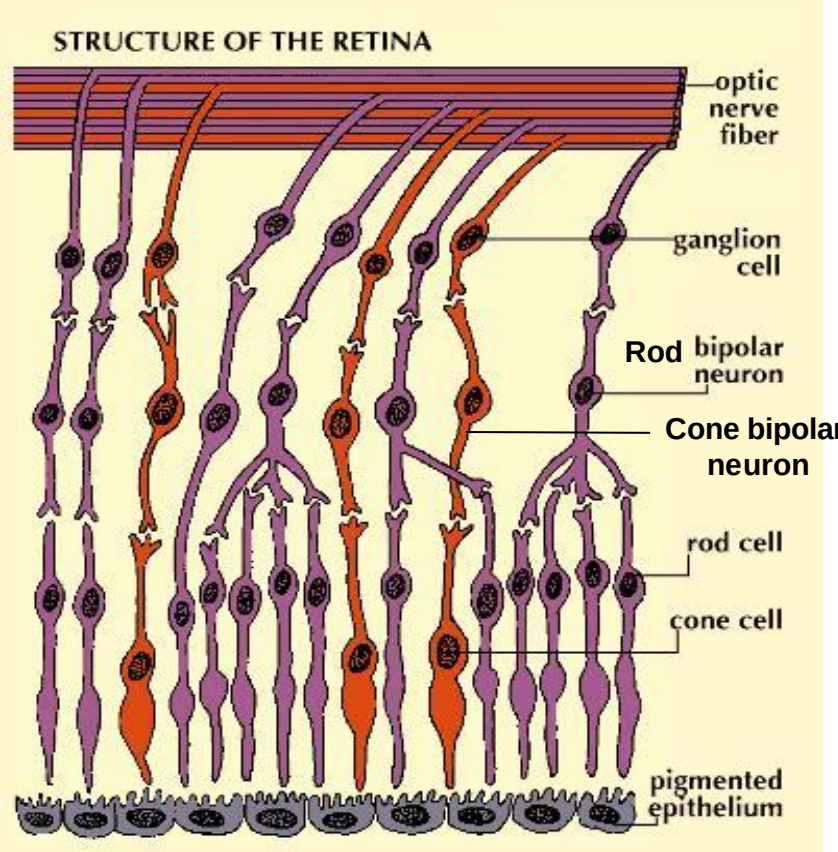
Distribution of Rods & Cones across Retina







Synaptic pattern of Photoreceptors



High degree of convergence reduces resolution in rod system, whereas 1:1 relationship of cones to bipolar and ganglion cells increases the resolution or visual acuity.

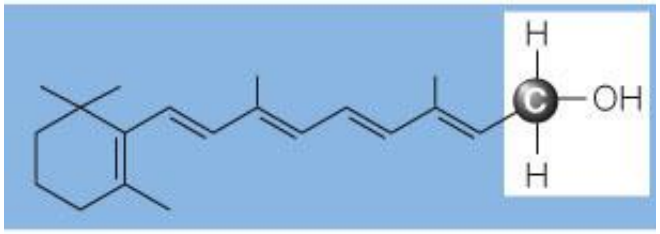
Rods vs. Cones

Rods	Cones
Used for scotopic vision (vision under low light conditions) or night vision	Used for photopic vision (vision under high light conditions) or day vision
Very light sensitive	Not very light sensitive
Loss causes night blindness	Loss causes legal blindness
Low visual acuity (poor resolution) as many rods are connected to one bipolar cells showing a high degree of convergence	High visual acuity; better spatial resolution as each cone is connected to one bipolar cell
Not present in fovea	Concentrated in fovea
Outer segment is rod shaped	Outer segment is cone shaped
Confer achromatic or monochromatic vision	**Confer color vision (trichromatic vision)**
Stacks of membrane-enclosed disks are unattached to cell membrane directly	Disks are attached to outer membrane
About 120 million rods distributed around the retina (peripheral vision)	About 6 million cones distributed in each retina (central vision)
One type of photosensitive pigment (Rhodopsin)	Three types of photosensitive pigments in humans (blue, green and red cones)

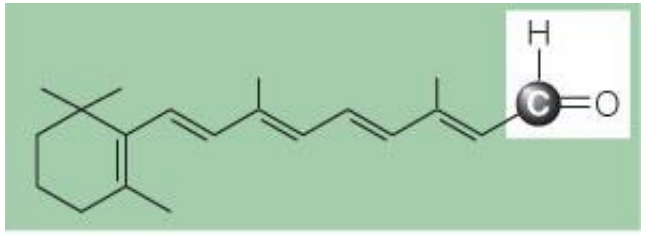
Vitamin A and Visual Cycle

- Vitamin A is one of the fat-soluble vitamins
- Derivatives of vitamin A (*preformed*): retinol, retinal (retinaldehyde), retinoic acid (the biologically active metabolite of vitamin A) and retinyl ester

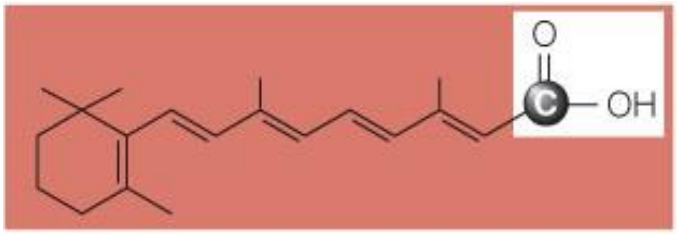
4 main forms of vitamin A



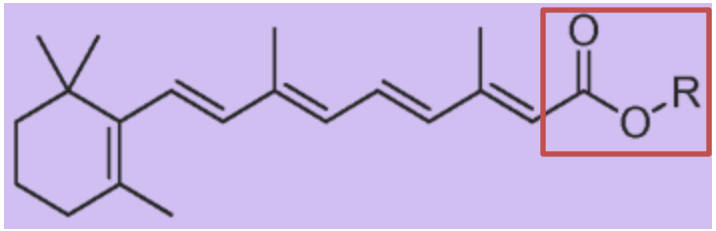
Retinol, the alcohol form



Retinal, the aldehyde form



Retinoic acid, the acid form



Retinyl ester, the ester form

- These preformed compounds are found in animal products as retinyl esters (e.g. liver, eggs, cod liver oil, meat, dairy products …. etc)

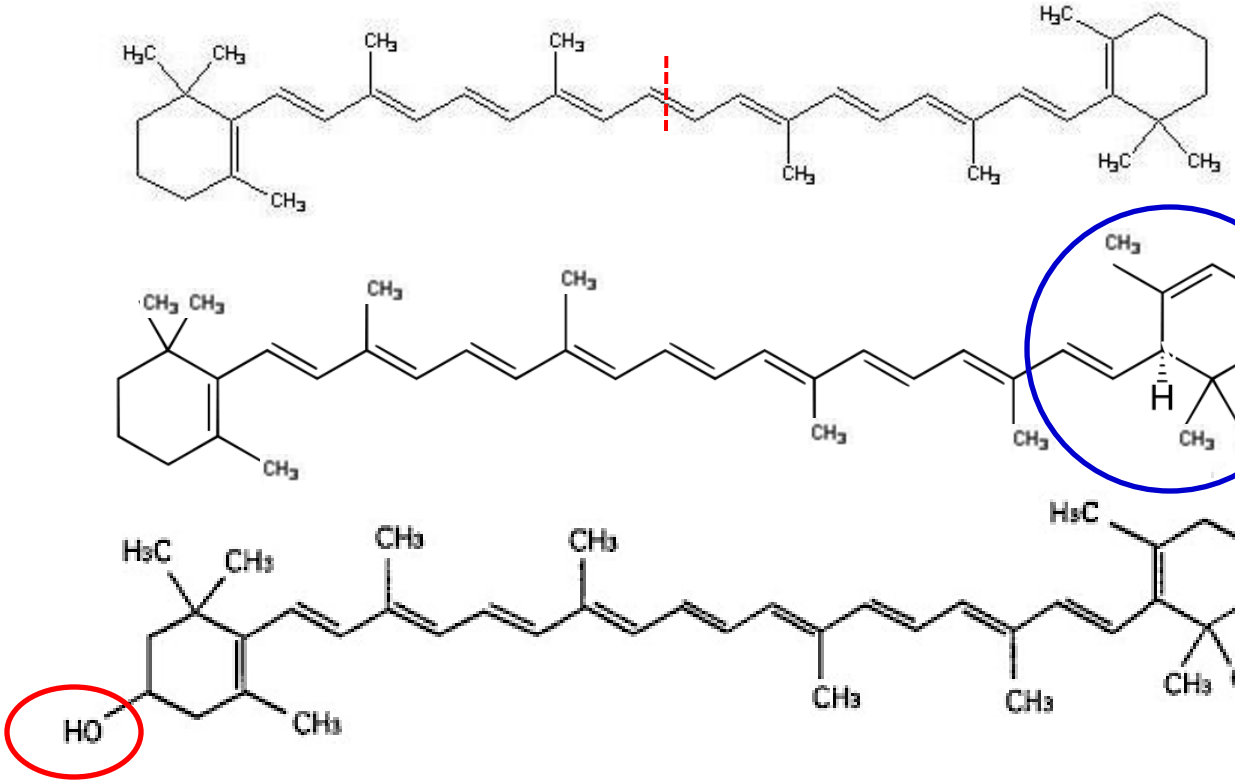
Vitamin A and Visual Cycle

- Retinoids: are a class of chemical compounds that are related chemically to vitamin A. They are widely used in medicine as they have diverse functions in the body
  - First generation: retinal, retinol, tretinoin (all *trans* retinoic acid, Retin-A) , isotretinoin (Roaccutane, UK and Accutane, USA) and alitretinoin

  - Second generation: etretinate and its metabolite acitretin
  - Third generation: tazarotene, bexarotene and Adapalene

Vitamin A and Visual Cycle

- Provitamin A: like some carotenoids which can be converted/ metabolized in the body to retinoids with vitamin A activity. They are found in plant sources (e.g. carrot)



Vitamin A and Visual Cycle

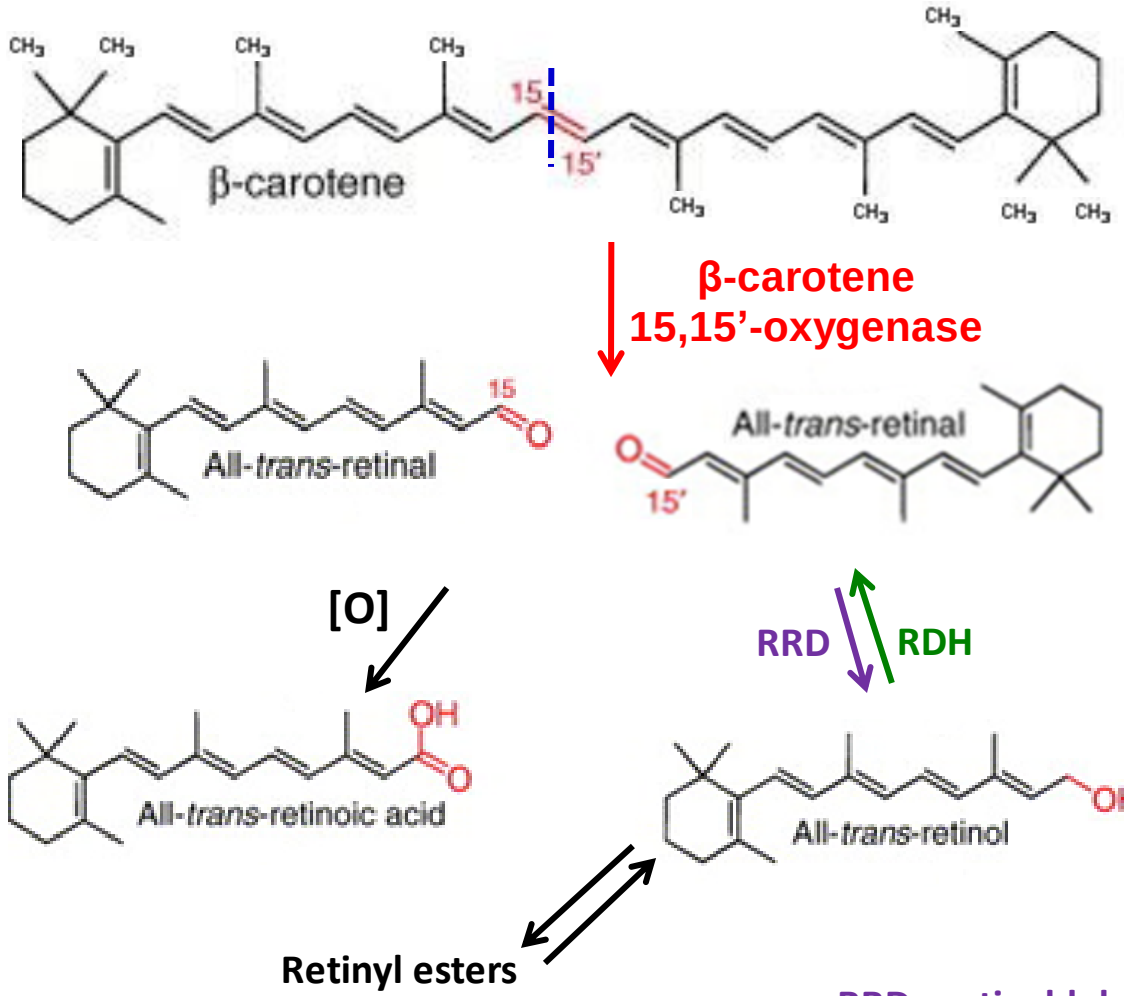
- Carotenoids: are organic pigments synthesized by plants and cannot be made by animals. Two classes:
  1. Carotenes: are responsible for the orange color of many vegetables & fruits (e.g. carrots and sweet potatoes) also for yellow color of milk-fat and butter (in low concentration). Some are provitamin A: like α-carotene (single retinyl group) and β-carotene (two retinyl groups)

  2. Xanthophylls: are yellow pigments. β-cryptoxanthin (provitamin A) is the only xanthophyll which possess vitamin A activity.

Carotenoids Absorption & Metabolism

- Only a limited amount of the provitamin carotenoids (plant sources) can be absorbed intact. These are stored in body tissues such as adipose cells of fat depots throughout the body. To date, the only side effect of excess beta-carotene supplementation appears to be yellowing of the skin.
- Carotenoids are largely converted to retinol (vitamin A) during intestinal absorption in the mucosal cell.

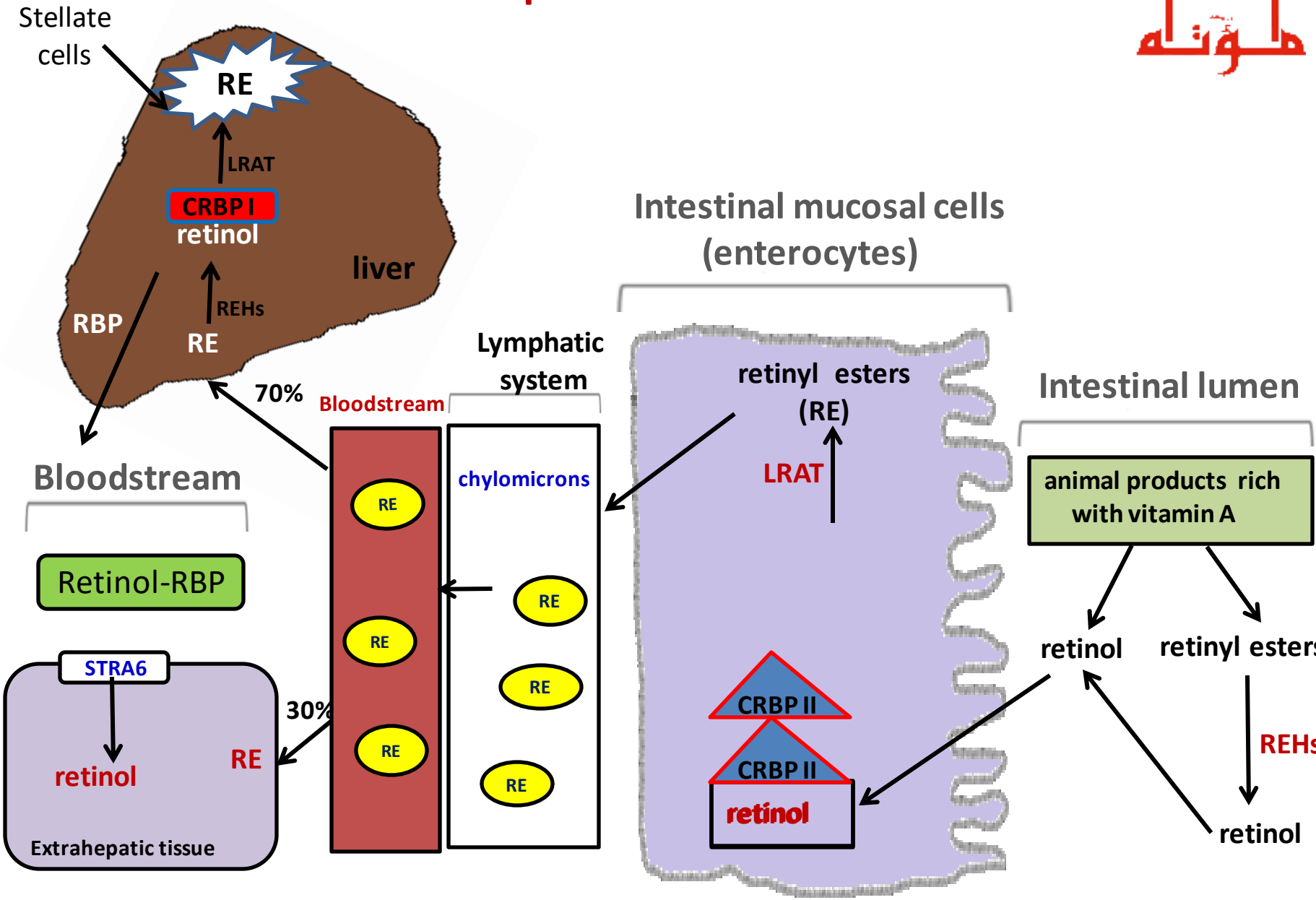
Hydrolysis of β-carotene



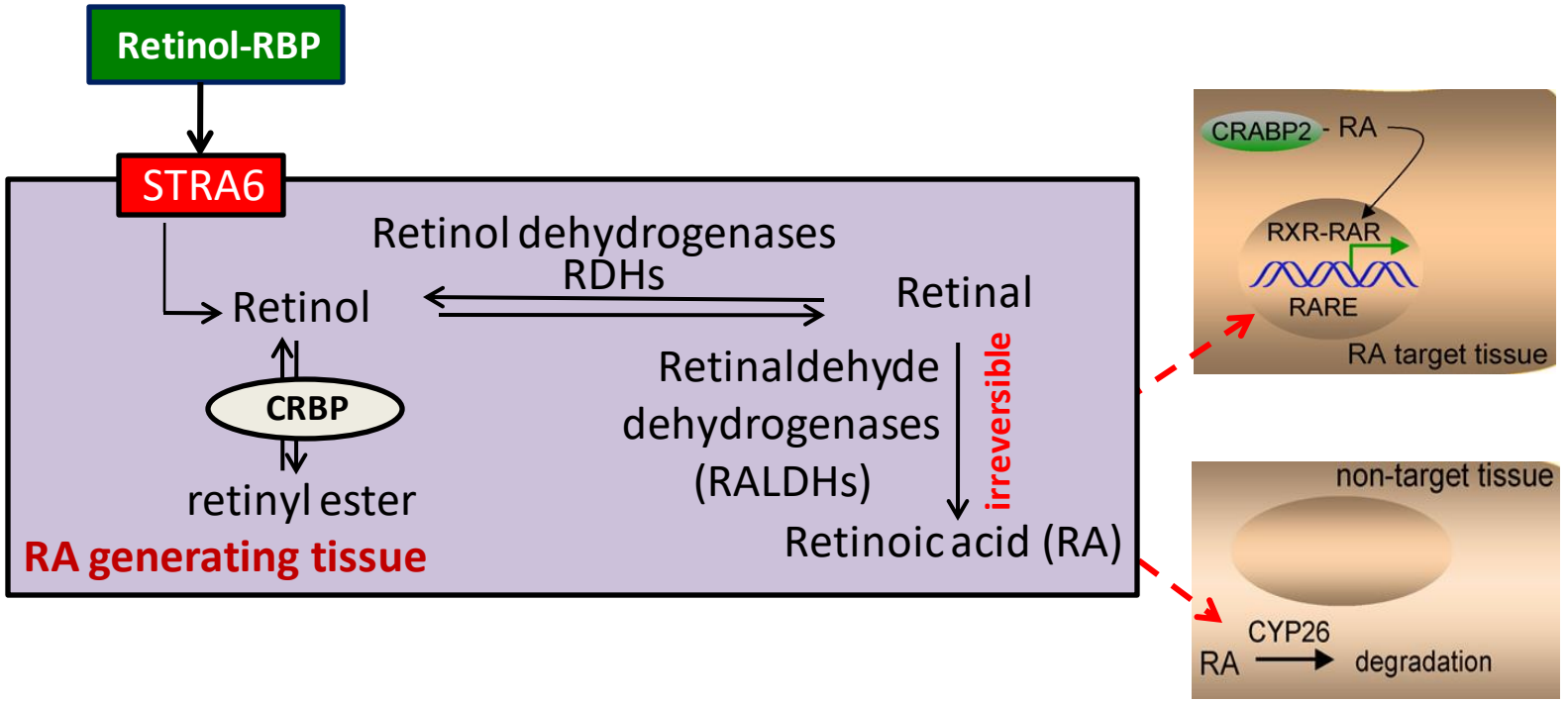
RRD: retinaldehyde reductase

RDH: retinol dehydrogenase

Vitamin A Absorption & Metabolism



Vitamin A Absorption & Metabolism



Vitamin A Absorption & Metabolism

- **REHs:** retinyl ester hydrolases like pancreatic triglyceride lipase the main enzyme responsible for the REH activity in intestinal lumen and hepatic lipase enzyme in hepatocytes
- **LRAT:** lecithin retinol acyl transferase
- **CRBPs:** cellular retinol binding proteins like **CRBPI** (ubiquitously expressed in tissues), **CRBPII** (primarily expressed in small intestine) and **CRBPIII** (predominantly expressed in adipose tissue, heart, muscle & mammary).
- **RBP:** retinol binding protein
- **STRA6:** stimulated by retinoic acid 6

Vitamin A Absorption & Metabolism

- Retinol is stored in several tissues particularly liver (as retinyl esters).
- Vitamin A is mobilized from liver stores and transported in plasma as retinol bound to a specific transport protein called retinol binding protein **"RBP"** (retinol is toxic, so, it is not let free and should be esterified or bound to RBP).
- Nonspecific and unregulated delivery of retinoids to biological membranes can lead to vitamin A toxicity.

Physiological Roles of Vitamin A

1. **Vision**: Vitamin A is a component of photopigments (rhodopsin & Iodopsins) in which **retinal** (the visual active form of vitamin A) is bound to the protein opsin. These play an essential role in the conversion of light energy into nerve impulses at the retina
2. **Gene transcription and embryonic development:** this role is played by **retinoic acid** form of vitamin A. RA binds its nuclear receptor RAR to regulate the transcription of its target genes

Physiological Roles of Vitamin A

- Therefore, **RA** influences the induction and patterning of some tissues at early stages of embryonic development
- Studies showed that **RA** is essential for development of several organs such as hindbrain, spinal cord, heart, eye…etc.
- Vitamin A is unique among the vitamins in that its concentration must be within a very narrow range in order to avoid both deficiency and toxicity
- Adding vitamin A or **RA** to embryo can easily induce teratogenic effects including major alterations in organogenesis (i.e. congenital abnormalities or birth defects)

Physiological Roles of Vitamin A

3. **Antioxidant**: carotenoids like **β-Carotene** protect the body from free-radical damage to DNA and cells to prevent diseases like cancer.
4. **Maintain skin health**: vitamin A, and more specifically, **retinoic acid**, appears to maintain normal skin health by switching on genes and differentiating keratinocytes (immature skin cells) into mature epidermal cells. The retinoic drug isotretinoin (**Ro-accutane®**) is the most commonly prescribed agent for treatment of acne.
5. **Reproduction**: **retinoic acid** (RA) supports both male and female reproduction. RA plays a vital role during the spermatogenesis (the process of production of sperm cells). In females, vitamin A is important to maintain normal fertilization, implantation and to overcome fetal resorption or malformation

Physiological Roles of Vitamin A

6. **Bone growth:** vitamin A is important for healthy bones. However, excessive amounts of vitamin A have been linked to bone loss and an increase in the risk of hip fracture. Indeed, too much **retinoic acid** affects the process of bone remodeling because it:
    - activates bone resorption by increasing the number and activity of osteoclasts (the cells that break down bone).
    - decreases the growth of osteoblasts (the cells that support bone growth)

Vitamin A Deficiency

- Vitamin A is stored in the body so it would take a year or more to develop a deficiency in the presence of inadequate intake.
- Vitamin A deficiency (Hypovitaminosis A):
  1. Infectious diseases due to impaired immunity
  2. Night Blindness (Nyctalopia): patient cannot see in dim/low light or near darkness conditions. Nyctalopia is first detectable sign of vitamin A deficiency.
  3. Complete blindness in severe deficiency.
  4. Xerophthalmia: dryness of the conjunctiva and cornea. If untreated, it can lead to corneal ulceration and keratomalacia (softening and necrosis of the cornea due to severe VAD)
  5. Keratinization of the skin: changes in epithelial cells results in keratinization, rough dry and scaly skin.

Vitamin A Toxicity

- Vitamin A toxicity (Hypervitaminosis A): can occur with concentrated amounts of vitamin A from animal foods, fortified foods, or supplements or consuming excessive amounts of β-carotene from supplements.

1. Bone defects: increased activity of osteoclasts causes weakened bones and contributes to osteoporosis and fractures
2. Birth defects: abnormal fetal development and malformation.