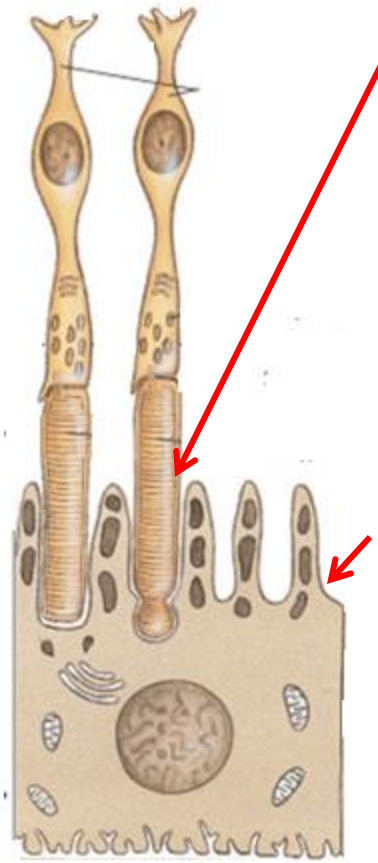
Vision ⇒ dependent on retinal

Regeneration of Visual Pigment



Rod outer segment

Retinal Pigment Epithelium

H_2O

Rhodopsin

all-trans retinal

all-trans retinilidene

retinol dehydrogenase

all-trans RDH

Reduction ↓ give H^+ ion

hν in the presence of light

all-trans retinol

11-cis retinilidene

Rhodopsin

all-trans retinol

11-cis retinal

oxidation

LRAT

esterification

11-cis RDH

Rate limiting step

RPE65

reduction

all-trans retinyl ester

11-cis retinol

to provide chemically stable storage form of vit A

prerequired step before isomrization

outer segment

Regeneration of Visual Pigment

↳10 – 45 min

- 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 (retinal ⇒ conjugated system) 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

regeneration of iodopsin Cons faster than rods Rhodopsin

- 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).

     Cons → rods
  2. Light adaptation: is the adaptation to increased level of illumination (i.e. when you move from the dark to the light, 5 min).

     rods →

     Cones
- 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

     ↓ time consuming step

Photoreceptor cells

Retina contains two types of photoreceptors:

rods # 20 times more than can

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

↓ High degree of convergen

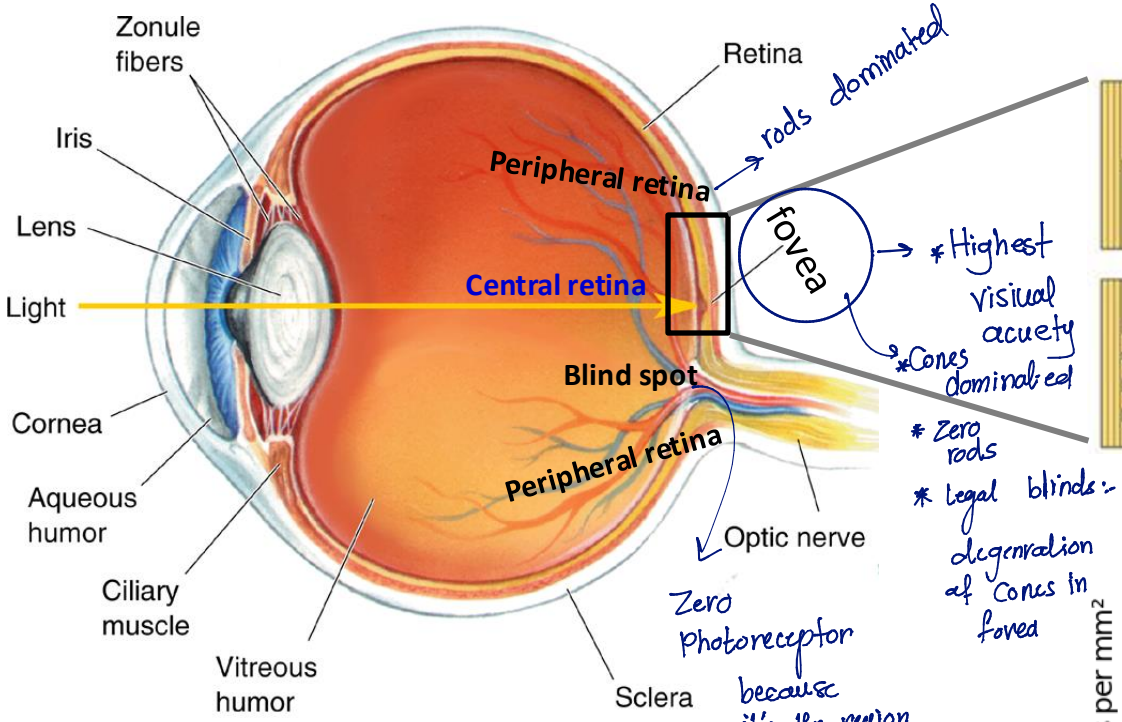
2. Cone cells: about 6 million, function in bright light (daytime vision)and are responsible for color vision, with low sensitivity and high resolution

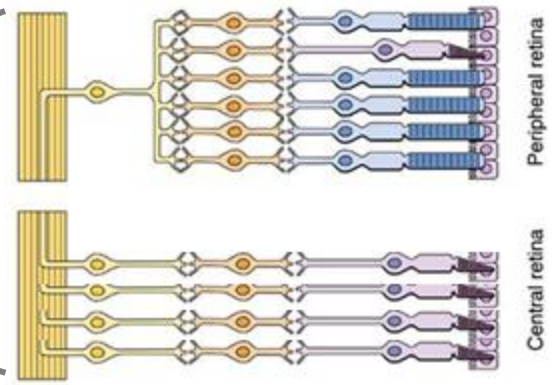
⇓ Need bright light to be stimulated

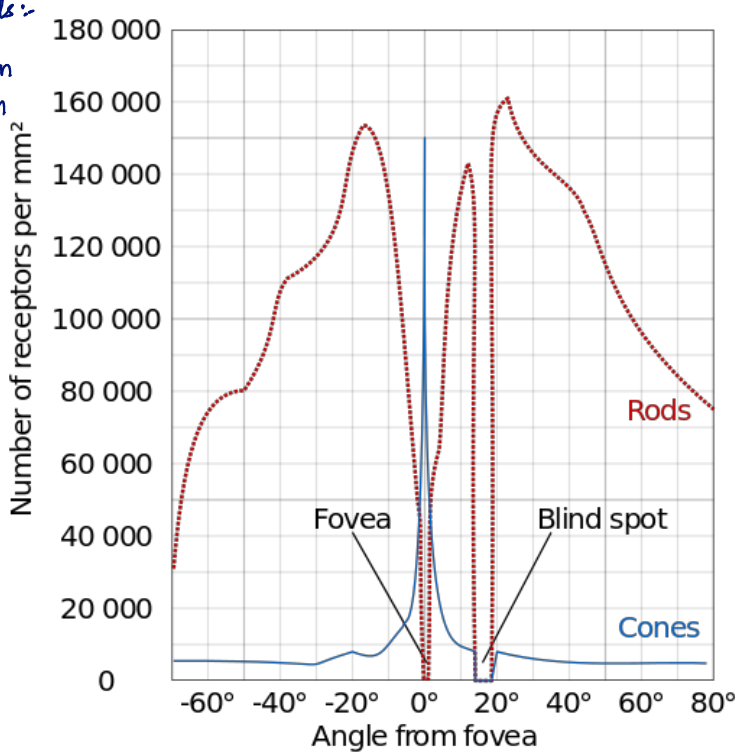
* visual acuety
* Sharp vision

← due to low degree of convergen 1:1

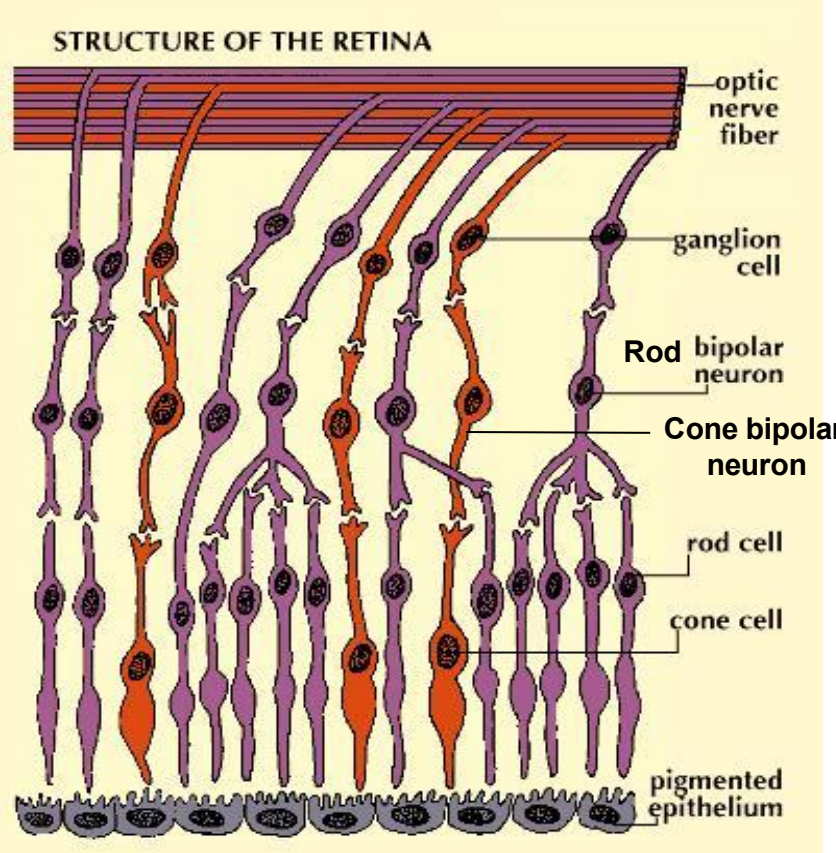
Distribution of Rods & Cones across Retina







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 (night-time) vision (vision under low light conditions) or night vision	Used for photopic (day-time) vision (vision under high light conditions) or day vision
Very light sensitive	Not very light sensitive
Loss causes night blindness (العشا الليلي)	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 (B & W) 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)

Animal Source for Vit.A ⇒ liver

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

main biologically active form of Vit.A in extraocular organ

Active form in retina

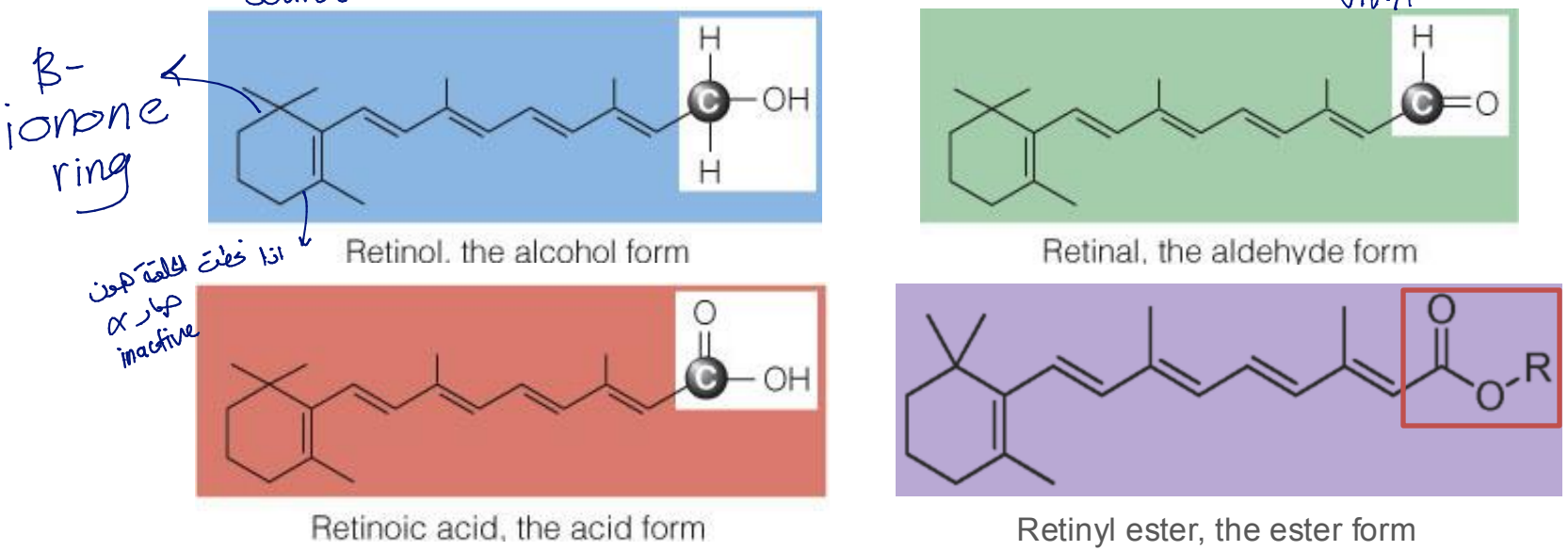
→ Chemically Stable

Storage form

4 main forms of vitamin A

In animal Source

"Preformed Vit.A"



- 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

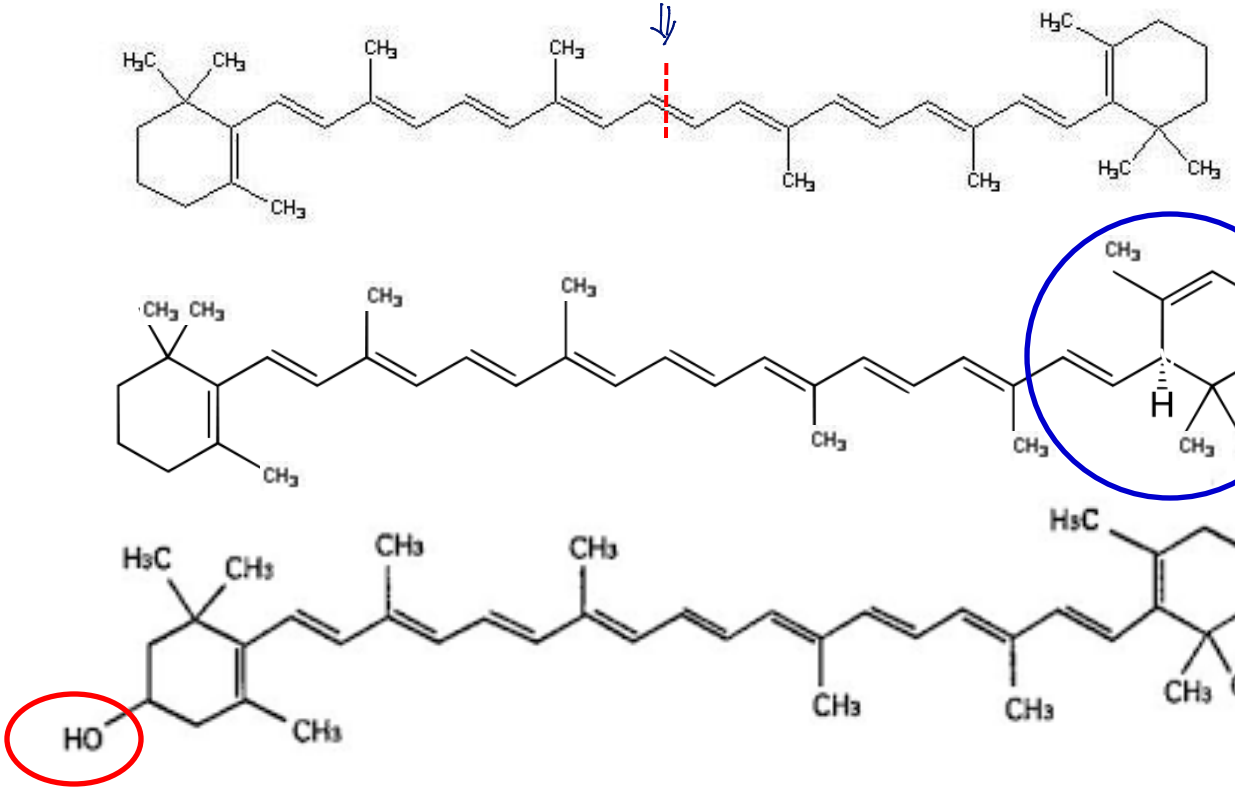
  - First generation: retinal, retinol, tretinoin (all *trans* retinoic acid, Retin-A) , isotretinoin (Roaccutane, UK and Accutane, USA) and alitretinoin

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

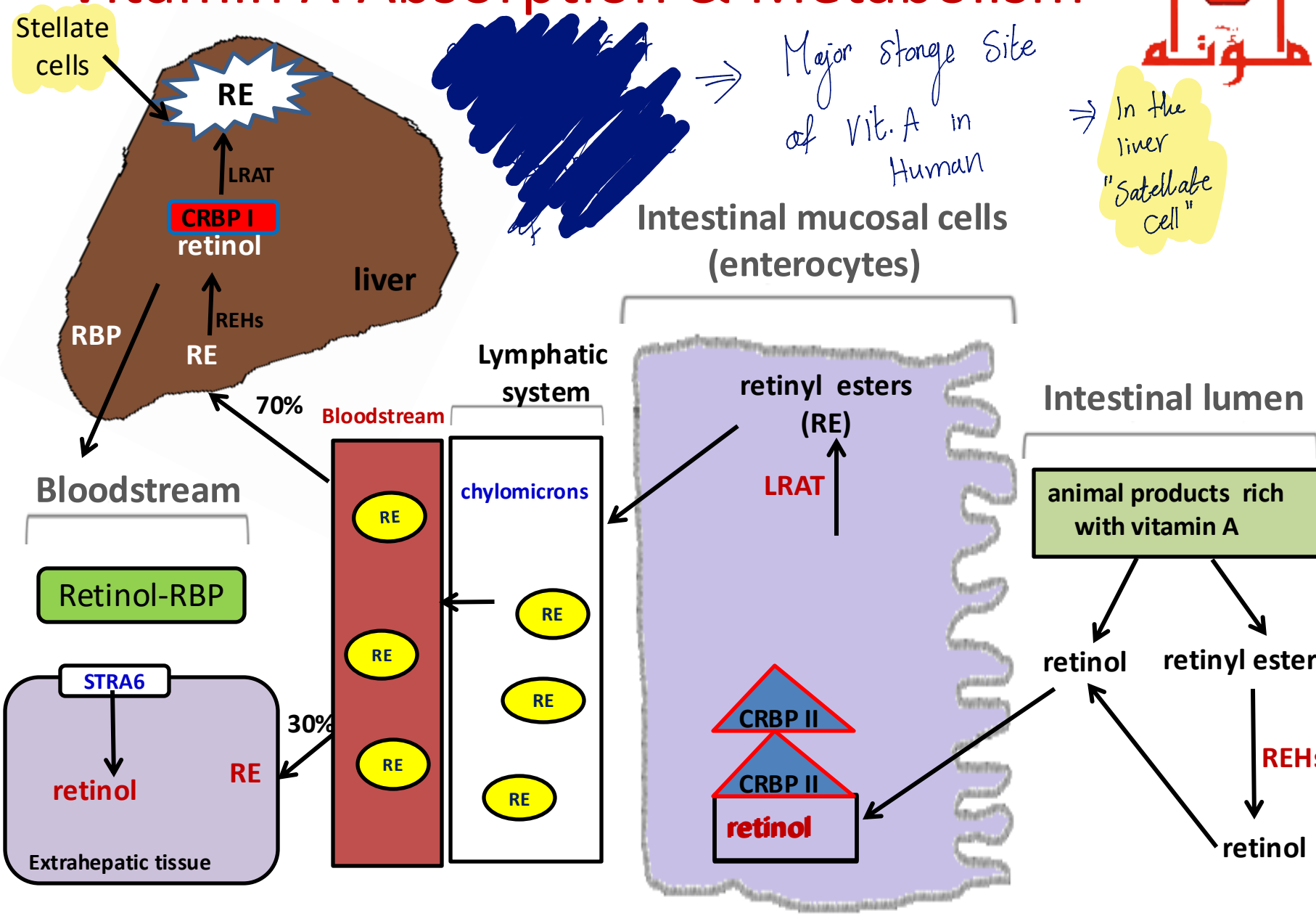
Vitamin A and Visual Cycle

Should be metabolized to be active

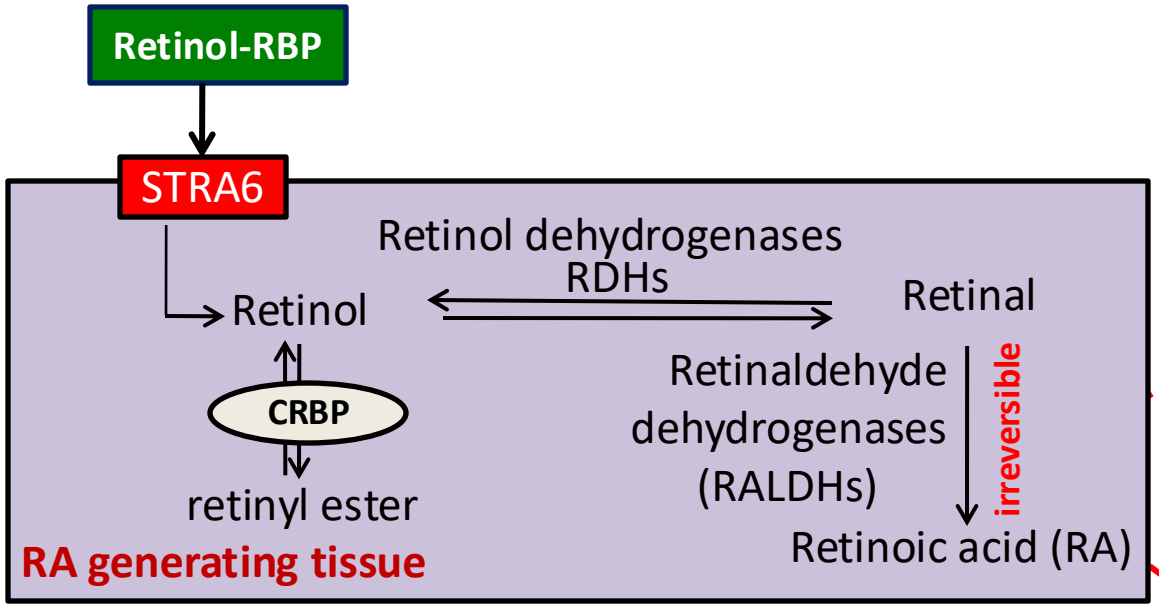
- **Provitamin A**: like some carotenoids which can be converted/ metabolized in the body to retinoids with vitamin A activity. They are found in plant sources (e.g. carrot)

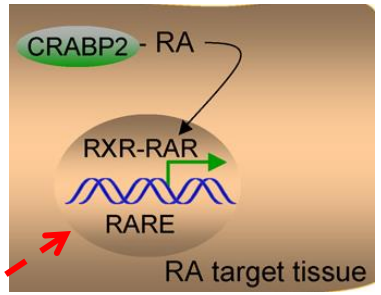


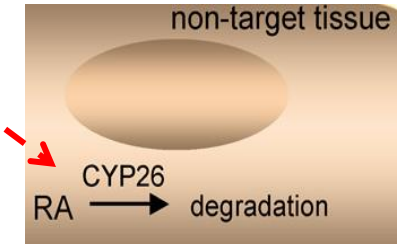
Vitamin A Absorption & Metabolism



Vitamin A Absorption & Metabolism







Vit. A ⇒ profound effect

تشتح هاي السالديد
هون

Vit. A ⇒ Retinoic acid "In the tissue"

↓

In the Retinoic acid generating tissee Retinol converted to → Retinal → Rutinoic Acid

انزايم مش معلوب نعرفه ↑

Converted to

↓ "مهم"

مجرد الخلية اخذت قرار بتحويل Retinol الى RA

ما بقدر يرجع RA يتحول لاي شكل تاني ∵ لـ Irreversible

Nucleur Receptors

RA - receptors في In the pNA

↓

Bind to Recepter

Control the transcription of other target Gene :-

↓

responsible

- Health
- renewel of skin
- Bone growth
- development of embryonic tissue

Non - target tissue

↓

degraded

target tissue

↓

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)