وَقُل رَّبِّ زِدْنِي عِلْمًا

النادي الطبي

PERIPHERAL NERVOUS SYSTEM

SUBJECT : Biochemistry

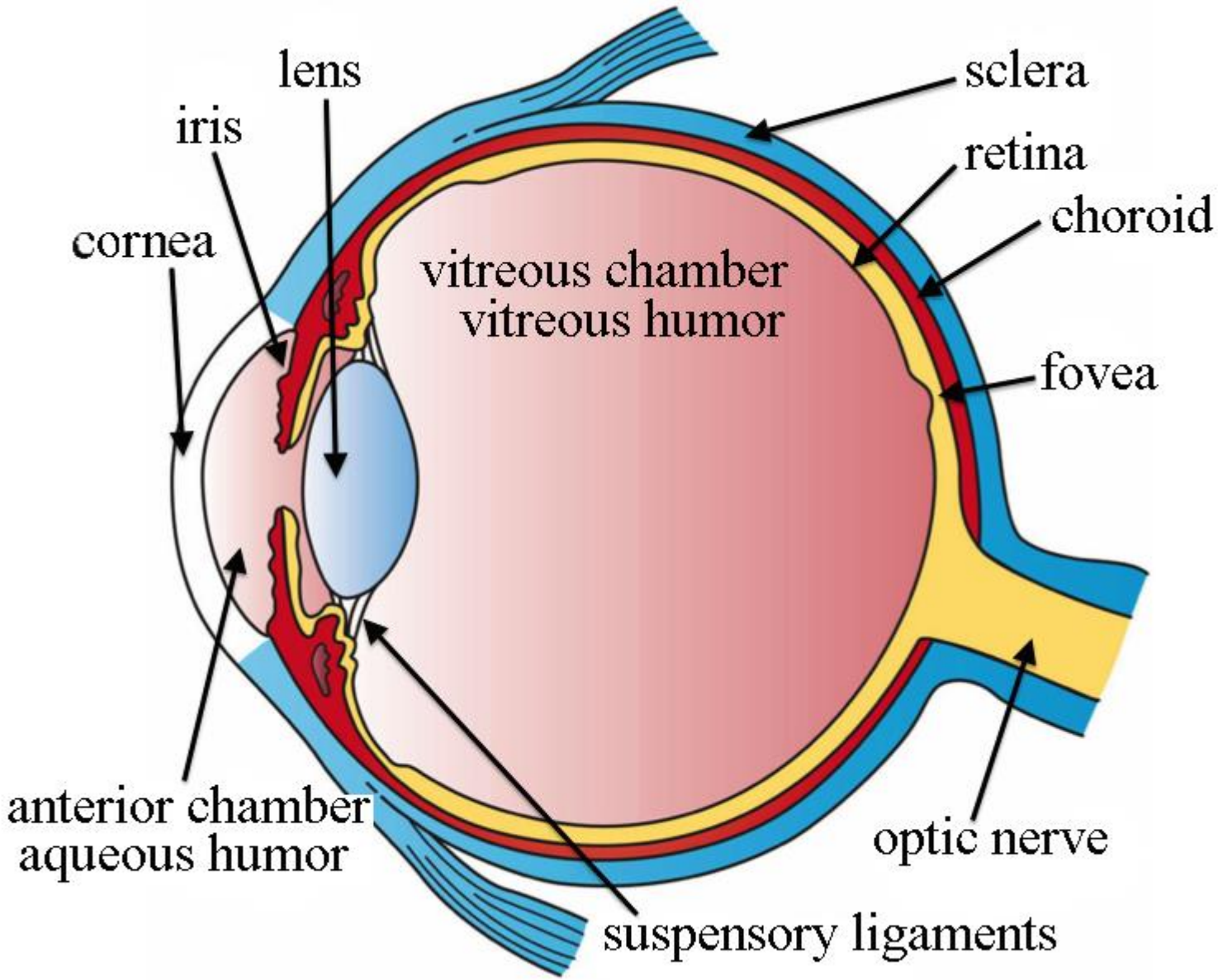
LEC NO. : 1

DONE BY : Batool ALzubaidi

#كلينيكال_إلا_شحطة

Biochemistry of vision

Ahmed Salem, MD, PhD, FRCR


lens
iris
cornea
sclera
retina
choroid
vitreous chamber
vitreous humor
fovea
anterior chamber
aqueous humor
optic nerve
suspensory ligaments

Vitamin A intro

- Vitamin A is needed by the retina in the form of a specific metabolite called **retinal** (vit A aldehyde) this is light absorbing
  - Necessary for low-light (scotopic) & colour vision

يعني لما تشوف بمكان ما فيه ضو كتير او لما بدك تشوف الالوان

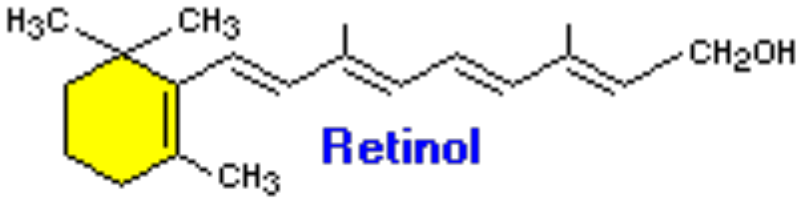
- Vitamin A also functions in a very different role as an irreversibly oxidized form of **retinol** (vit A alcohol) known as **retinoic acid** (vit A acid) which is an important hormone-like growth factor for epithelial and other cells

- **Vitamin A is present in 3 forms:**
  - Retinal
  - Retinol
  - Retinoic acid

من العرف انه الجزر فيه كتير فيتامين a هلا هو اكيد فيه بس كمصدر اساسي لازم يكون من مصادر حيوانية

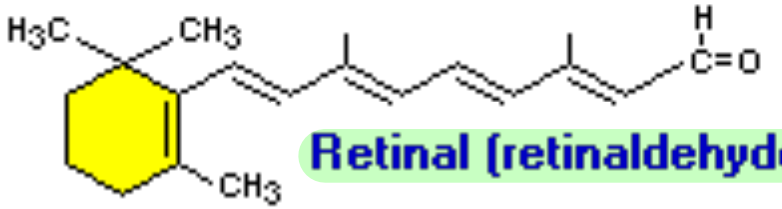
- Beta carotene is a pro-vitamin which is yellow to orange fat soluble pigment → vitamin A activity of beta carotene is 1/12 of retinol

هو الي بيعطي الجزر اللون الاورانج تاعه



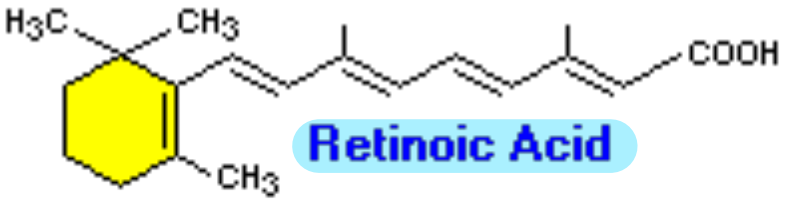
Retinol

Function: reproductive system



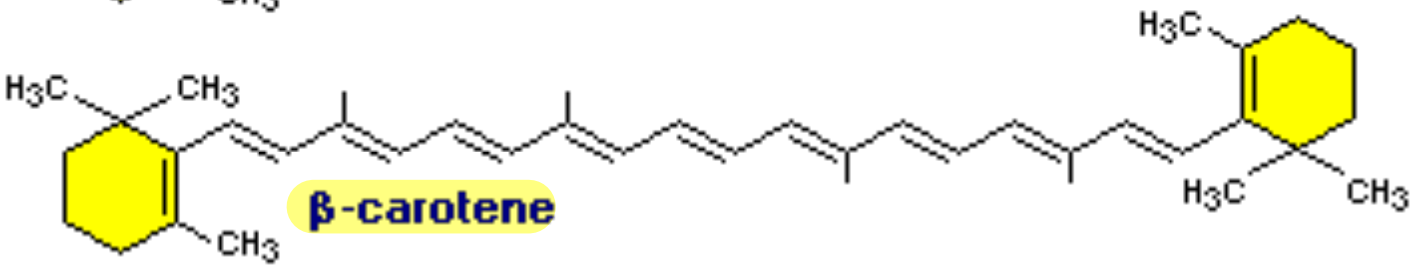
Retinal (retinaldehyde)

Function: vision



Retinoic Acid

Function: growth & differentiation



β-carotene

Function: pigment +
anti-oxidant properties

Vitamin A info

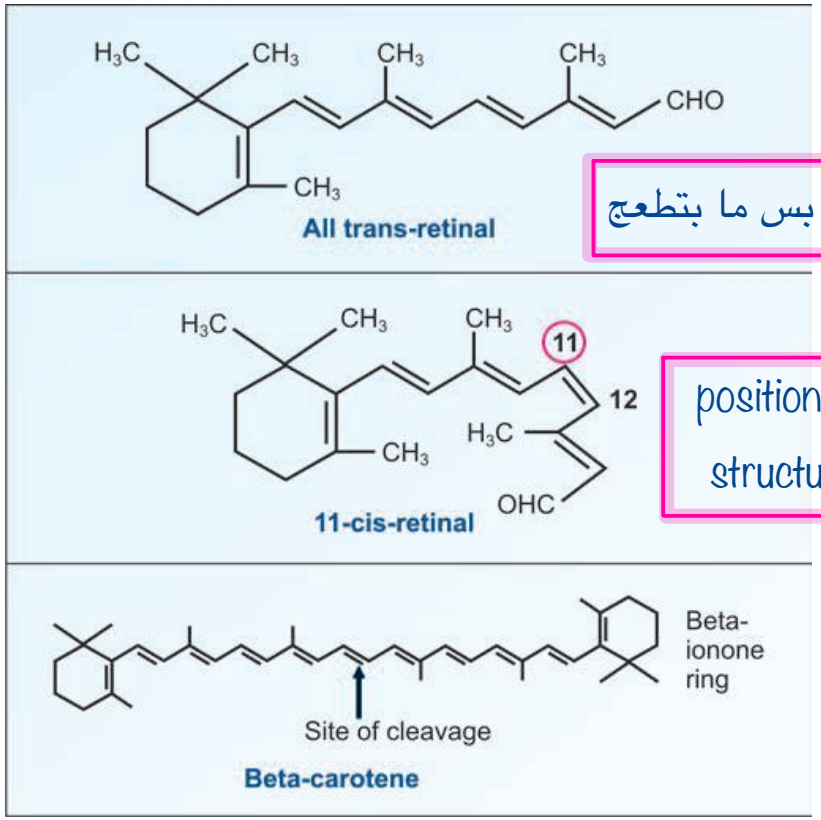
- Retenoids:
  - Source: animal tissues as cod liver oil, liver, kidney, butter

- Carotenoids: in both animal and plant sources as carrots

الدكتور مهتم بمادته مو بالفسيو بهمه جانب البيوكم فقط

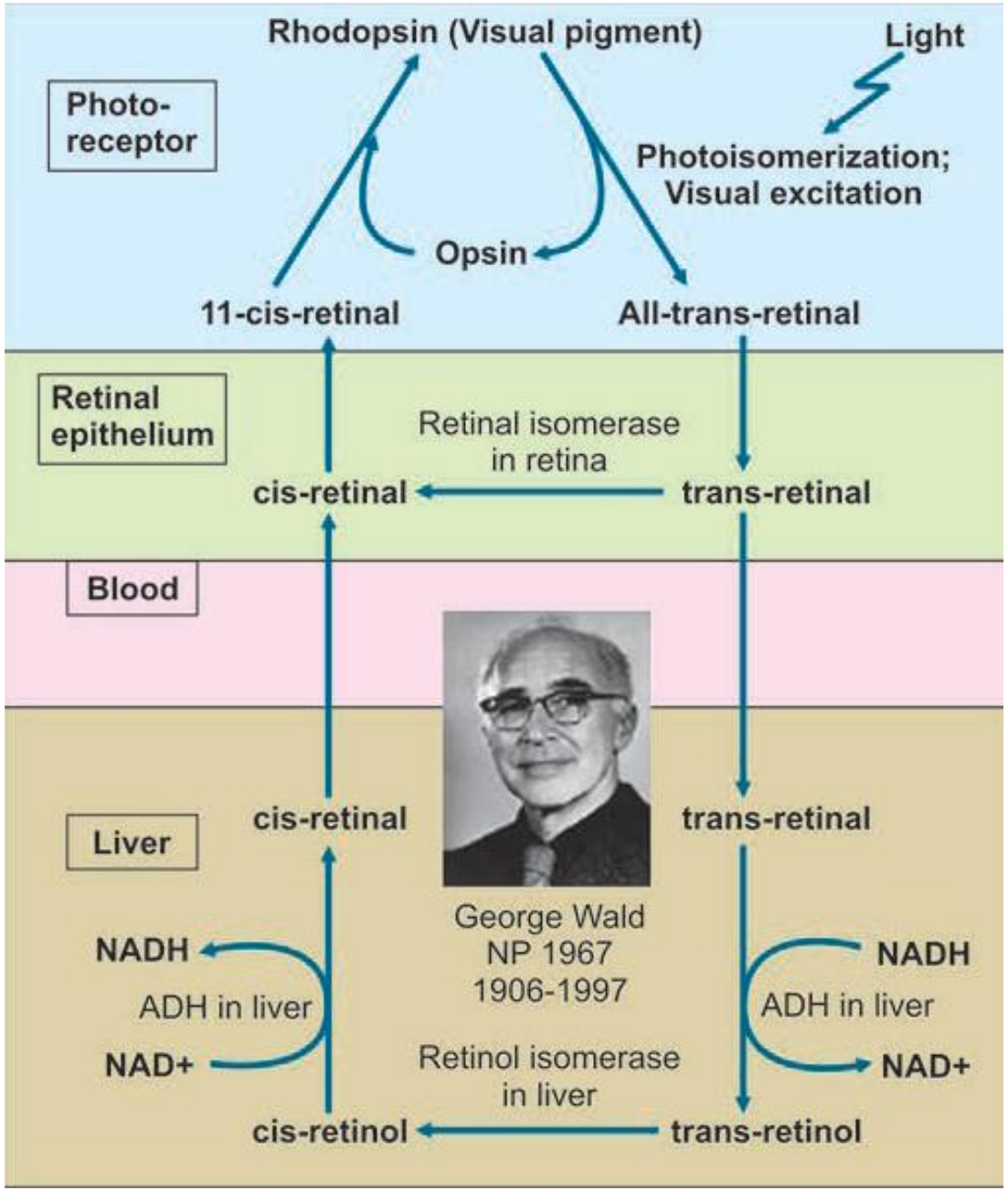
Role of vitamin A in vision

- 11-cis retinal is reversibly associated with the protein opsin in the rod cells of the retina → **visual pigment (rhodopsin)**

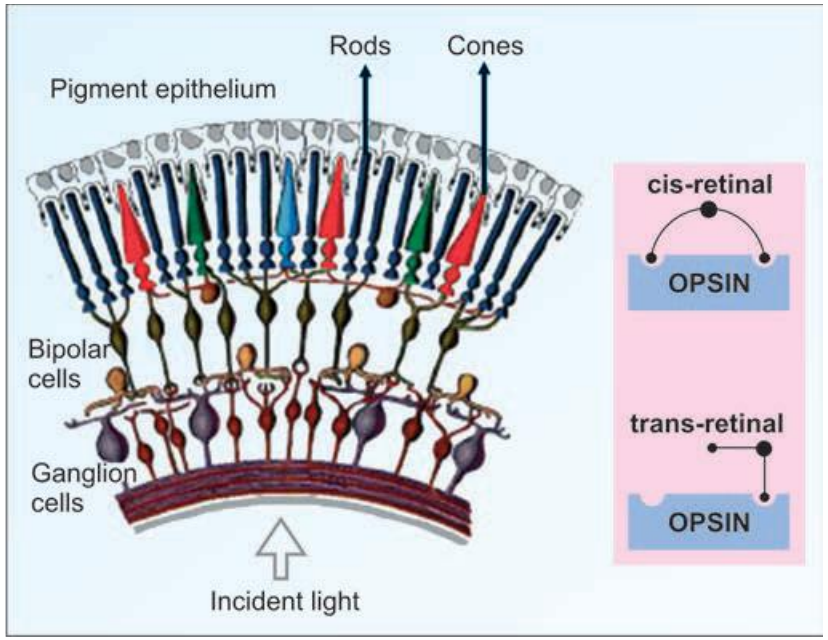


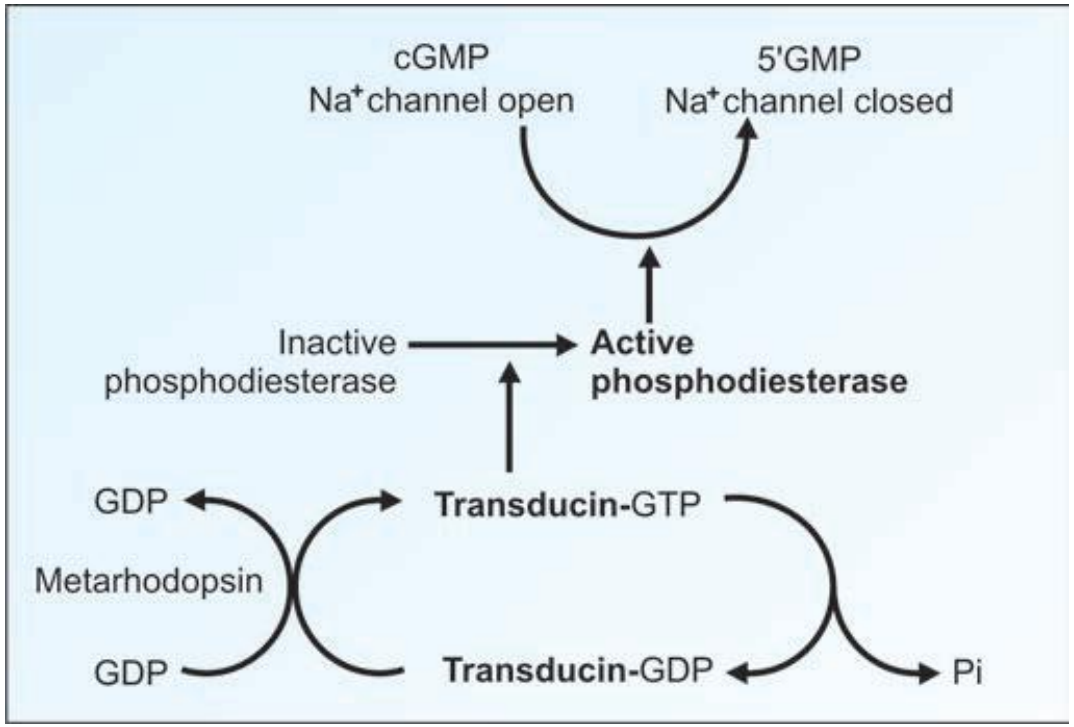
فيه double bonds بس ما بتطعج

في على position 11 double بتطعج ال bond structure



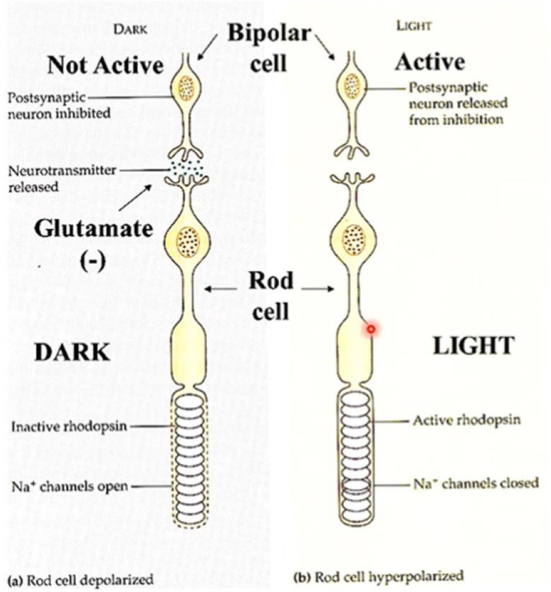
Generation of Nerve Impulse





Metabolism in the Retina

Principles of Phototransduction



cGMP keeps the ion-channel gates open!

Open gates = depolarization!

Released glutamate inhibits bipolar neurons

When it is **dark**, lots of cGMP → cGMP bound to rod membrane and gates kept open → inflow of cations → **depolarized** membrane → glutamate neurotransmitter release

When it is **light**, cGMP is lacking → gates are closed → no inflow of cations → **hyperpolarized** membrane → no glutamate neurotransmitters released

الضوء لما يفوت عندك بمر بطبقات ال retina بعدين بال ganglion cells بعدين ال bipolar cells بعدين pigment الي هم ال rods and cones ال rods مسؤولين عن النظر بالاماكن العتمة و ال cones مسؤولين عن ل color vision and high detailed vision

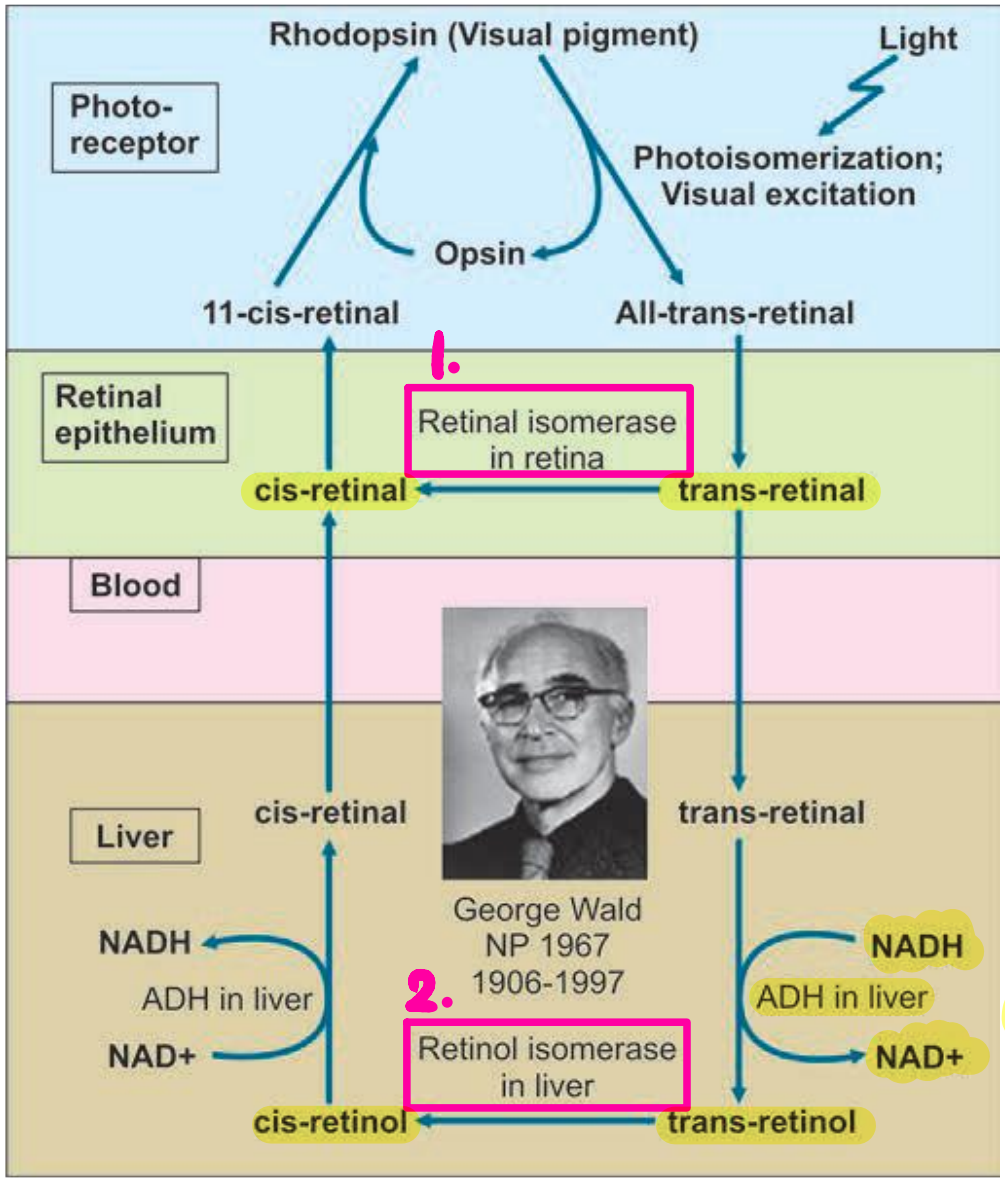
هلا احنا حكينا انه عنا نوع معين من vitamin a المسؤول عن النظر الي هو ال retinal و طلع في منه اكتر من نوع حسب ال double bond راح يطعج ال structure او لا الي هم ال cis / trans

هلا الضو لما يفوت بكون على شكل فوتونات و هاي راح تخبط ال visual pigment الي هي مكونة من شغلتين بروتين اسمه opsin و من retinal، ال retinal قبل ما يجي الضوء بكون على هيئة 11cis لما يجي عليه الضوء بصيرله photo-excitation بحوله ل all trans retinal و هاد بفتحلك signal transduction pathway .. عشان نعرف كيف بكون ال initiation لهاد ال pathway بدنا نتفق على بعض القوانين مع بعض اولا عنا cyclic GMP لما يكون عالي بفتح ال Na channels و يصير depolarisation راح ينتج glutamate و راح توقف ال signal pathway (طريقة كيف بوقف التوصيل مش مهمة)

لما ما يكون في ضوء ال retinal بكون على شكل cis و هيك كانه بكون ال molecule inactive و بصفي انت ما عندك transducin و هيك بكون GDP بكون عالي cyclic GMP لانه ال phosphodiesterase ما بكون active

العكس صحيح لو كان عندك trans retinal بسبب الضوء راح يعمل reactions بالنهاية بحولوا ال transducin GDP ل GTP transducin و راح يعمل activationto phosphodiesterase و راح يكسر cyclic GMP و ال channels بتسكر و بكون حالة hyperpolarisation و ما في glutamate و راح تكمل ال signal

Regeneration of 11-cis-retinal



في طريقتين بقدر اصنع من خلالهم cis retinal اولا
انزيم اسمه retinal isomerase هاد موجود بال
retina الي بحول all trans ل cis .. تاني طريقة
retinol isomerase الموجود بال liver هاد بحول
cis retinol ل trans retinaol، كيف بدي اصنع
retinol ؟؟ بال liver بحول ال trans retinal to
trans retinol بوجود NADH and zink و انزيم
ADH و بعد ما تصنع cis retinol بترجع بتحوله بال
liver بنفس الانزيم بوجود NAD+ ل cis retinal

Zinc

Dark Adaptation Mechanism

- Bright light depletes stores of rhodopsin in rods
- Therefore when a person shifts suddenly from bright light to a dimly lit area, there is difficulty in seeing
- After a few minutes, rhodopsin is resynthesized and vision is improved. This period is called **dark adaptation time**
  - It is increased in vitamin A deficiency
    - Rhodopsin present in rods is made up of 11-cis-retinal + opsin
    - Deficiency of cis-retinal will lead to increase in dark adaptation time and night blindness
- In humans → contains about 120-200 million rods, each of which carries 40-120 million molecules of rhodopsin
- The number of rods is more in cats, mice and owls

كمية ال rodes الموجودة عندك هي الي
بتحدد كم قوة انك تشوف بالليل

كل cone منهم موجود ب كروموسوم معين اشي منهم على كروموسوم ٧ و اشي منهم على كروموسوم X عشان هيك ال males يصابوا ب colour blindness اكتر من ال females

Cones for colour vision

- Cones are responsible for vision in bright light as well as colour vision
- They contain the photosensitive protein, conopsin
- There are 3 types of cones, each is characterized by a different conopsin, that is maximally sensitive to either blue (cyanopsin), green (iodopsin) or red (porphyropsin)
- In cone proteins also, 11-cis-retinal is the Chromophore
- Reduction in number of cones or the cone proteins, will lead to colour blindness
- One eye contains about 6 million cones

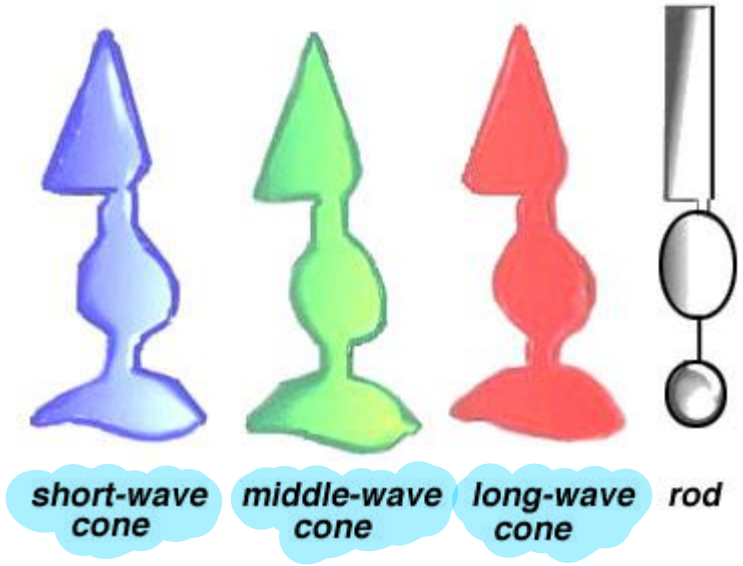
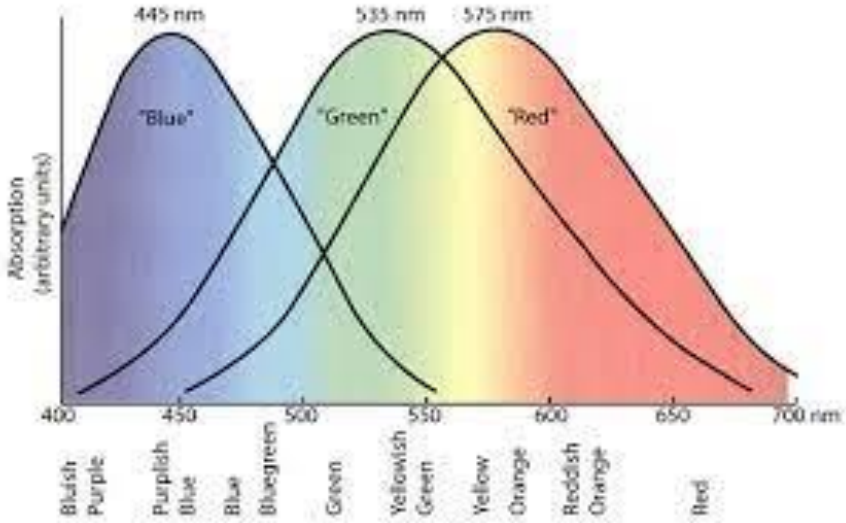


Fig. 13. There are four photoreceptor types in the human retina. Short-wavelength cones (blue), medium wavelength cones (green), long wavelength cones (red) and rods.



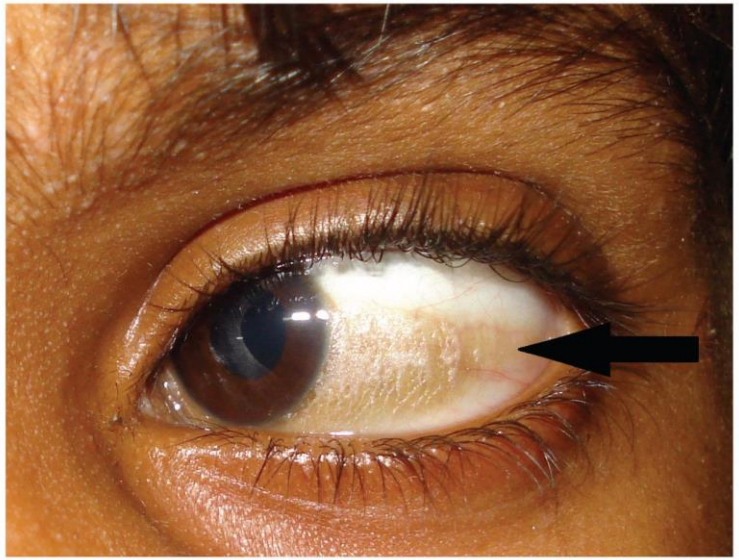
Colours have profound influence in life

- About one-third of grey matter of the brain is involved in the processing of visual information
- About 70% of information inputs to the brain are visual

For info only

- The optimists view the world through “rose-coloured” eyes
- When sad, a person is in a “blue” mood
- Saffron colour has tranquilizing effect, especially in agitated persons
- Mice living in red light are most active, while in green/blue light, they are least active

Deficiency manifestations of Vitamin A



- **Night Blindness or Nyctalopia**
  - Visual acuity is diminished in dim light
  - The patient cannot read or drive a car in poor light
  - The dark adaptation time is increased
- Xerophthalmia (conjunctiva is dry and thick)
- Bitot's Spots (greyish-white triangular plaques firmly adherent to the conjunctiva)
- Keratomalacia (softening of the cornea)

Before this step you can prevent progression to blindness by giving vitamine A

→**Preventable blindness**

→**About 40% of blindness is preventable (vit A is most common cause of preventable blindness)**

→**Vitamin A deficiency is a major public health problem**

How does cornea stay clear

How does the cornea stay clear?

The cornea must **stay clear in order to diffract light**. This is achieved through two mechanisms:

[1] **Avascular** state maintained by **VEGFR-3** to **prevent angiogenesis**

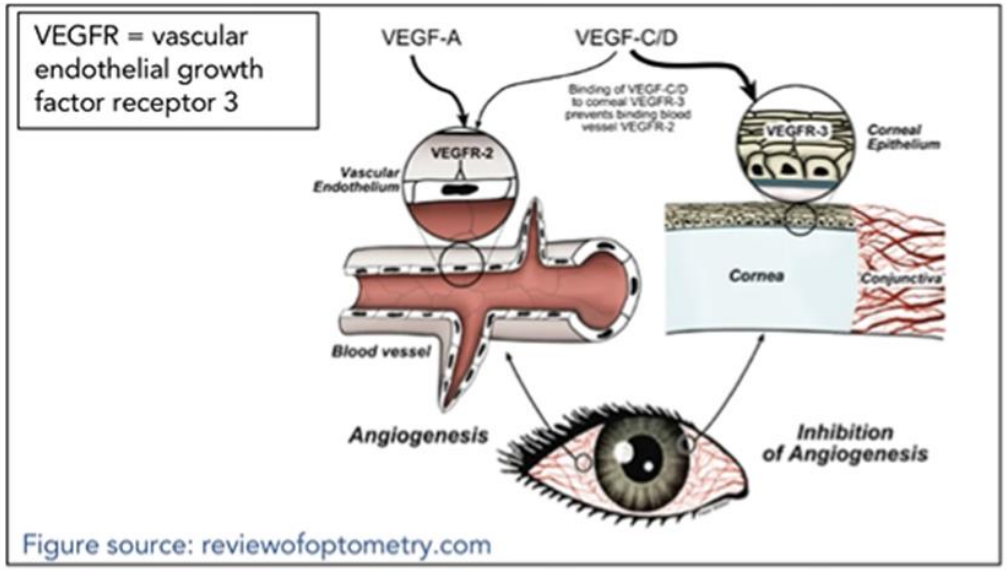


Figure source: reviewofoptometry.com

[2] **ATP-driven water pump** that controls the water content and clarity

In both cornea and lense

How does the cornea generate ATP?

Glucose Metabolism in the Cornea

- Glycolysis (30%)
  - **30%** glucose metabolised through aerobic and anaerobic (lactate mediated) **glycolysis**
- Hexose Monophosphate Pathway (60%)
  - **60%** glucose metabolized by **HMP pathway. Note that this pathway produces NADPH (a reducing agent)**

How does the cornea protect itself from reactive oxygen species?

How does the cornea protect itself from ROS?

The cornea is prone to reactive oxygen species (ROS) due to exposure towards atmospheric oxygen

ROS cause damage through:

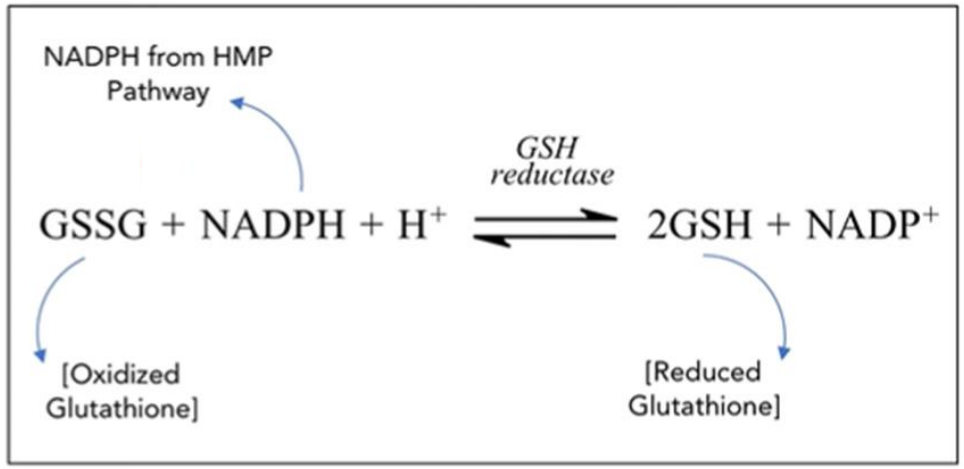
1. Lipid peroxidation
2. Protein oxidation

The cornea protects itself by neutralizing ROS using NADPH (produced from HMP pathway) which enhances the work of glutathione (GSH)

How does NADPH enhance GSH to neutralize ROS?

If an oxidant comes along, GSH takes the blow and gets oxidized. But too much oxidants may lead us to GSH deficiency

Therefore we need to **increase GSH production** by reducing GSSG through NADPH + GSH reductase



GSH = glutathione, GSSG = glutathione disulfide

Figure adapted from: Devlin, TM. 2011. **Textbook of biochemistry**. John Wiley & Sons

Biochemistry of the lens

How does the lens stay clear?

Main function is to **maintain clear crystallin state**

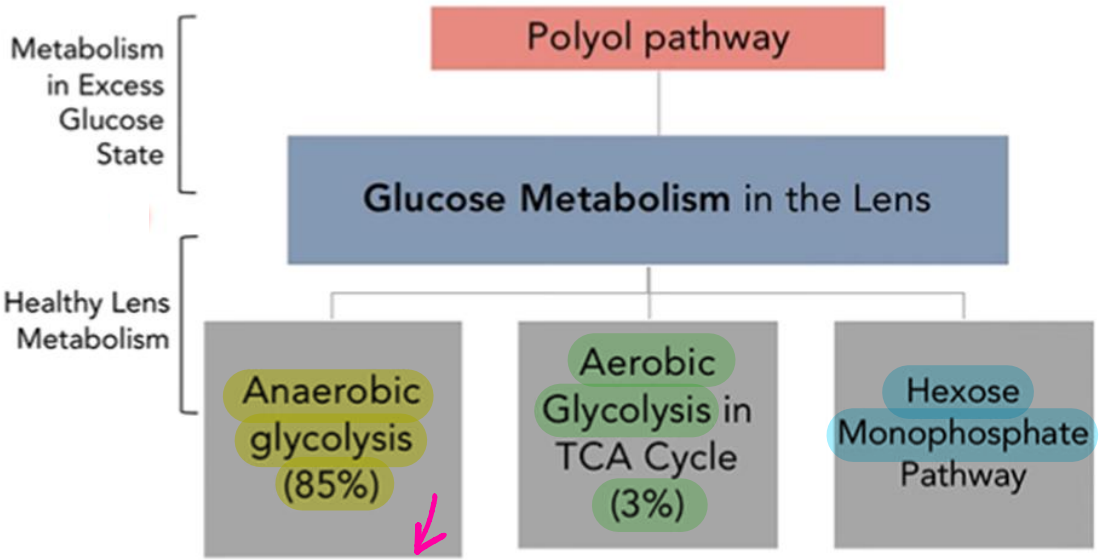
Osmotic balance regulated through **Na^+/K^+ ATPase**

Lens is **avascular** and is nourished by vitreous humour

Main components of the lens:

- **Water**
- **Proteins** α-, β-, γ- **crystallins** synthesized by the outer epithelial layer

How does the lens generate ATP?



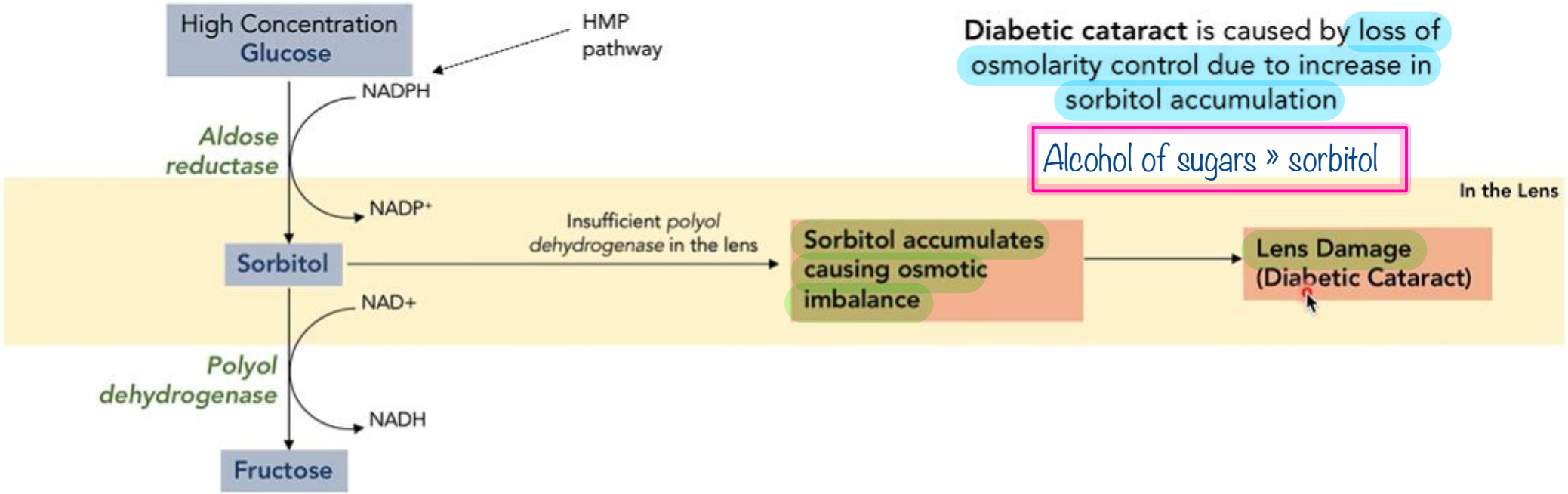
ال anaerobic glycolysis ال end product تاعه هو ال pyruvate و هاد acid هل منيح يضل بال lens اكيد لا طيب كيف بصيرله clearance وال lens is avascular ؟ الغذاء لل lens بيجي عن طريق vitreous فطبيعي ال lactic acid يطلع عن طريق ال diffusion و هو كميته بال lens اعلى من ال body و هاد ال concentration gradient احنا بحاجته عشان تضل تطلع ال lactic acid لبرة

Diabetic cataract

How is the polyol pathway activated?

The polyol pathway converts **glucose to fructose**

In the lens, the polyol pathway is activated in conditions of excess glucose (eg: diabetes)



How does polyol pathway cause diabetic cataract?

Cataract is a **disorder of lens opacity**

Senile cataract is caused by age-related changes in crystallin structure

Diabetic cataract is caused by loss of osmolarity control due to increase in sorbitol accumulation

Alcohol of sugars » sorbitol

Conclusions

- Vitamin A is very important for vision
- Cornea needs to protect itself from reactive oxygen species
- Lens: polyol pathway important in diabetic cataract