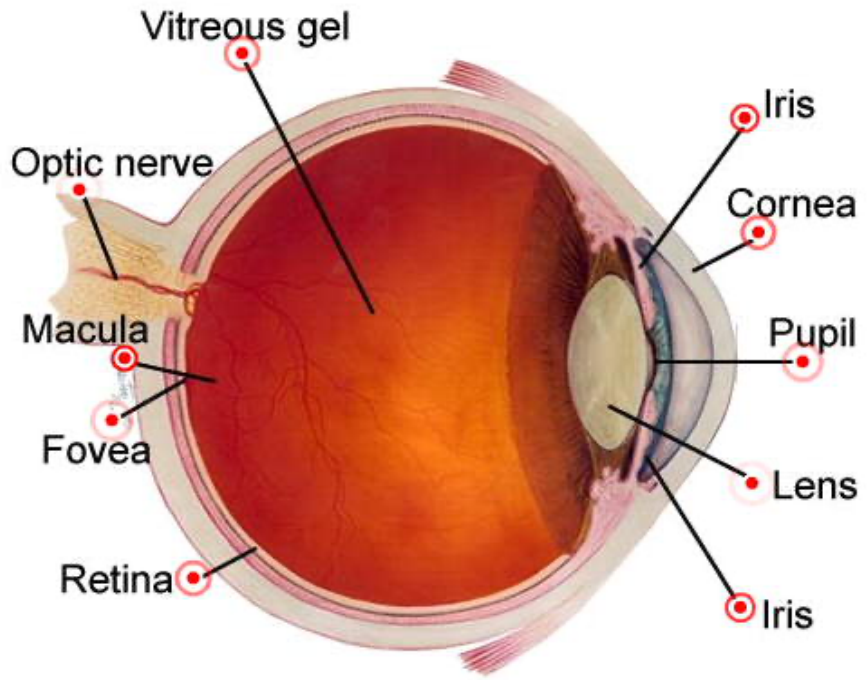
# PHARMACOLOGY OF DRUGS ACTING ON THE EYE

**Prof. Hanan Hagar**
**Pharmacology Unit**
**College of Medicine**



# ILOS

Outline common routes of administration of drugs to the eye.

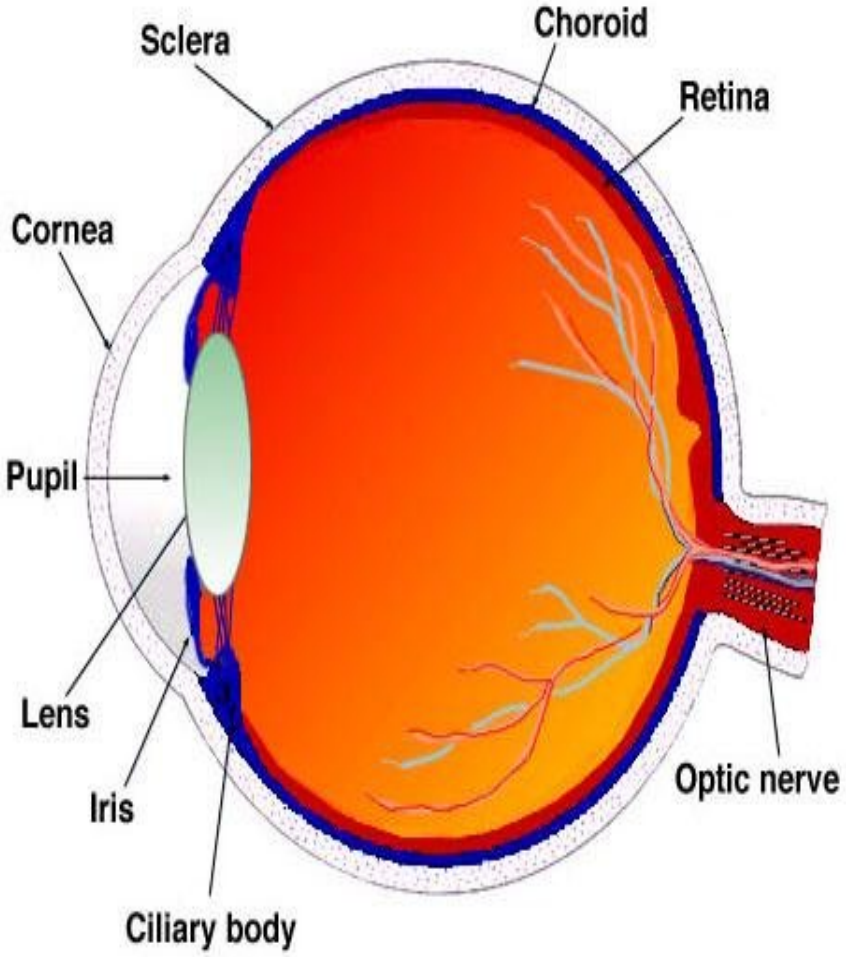
Discuss the pharmacokinetics of drugs applied topically to the eye.

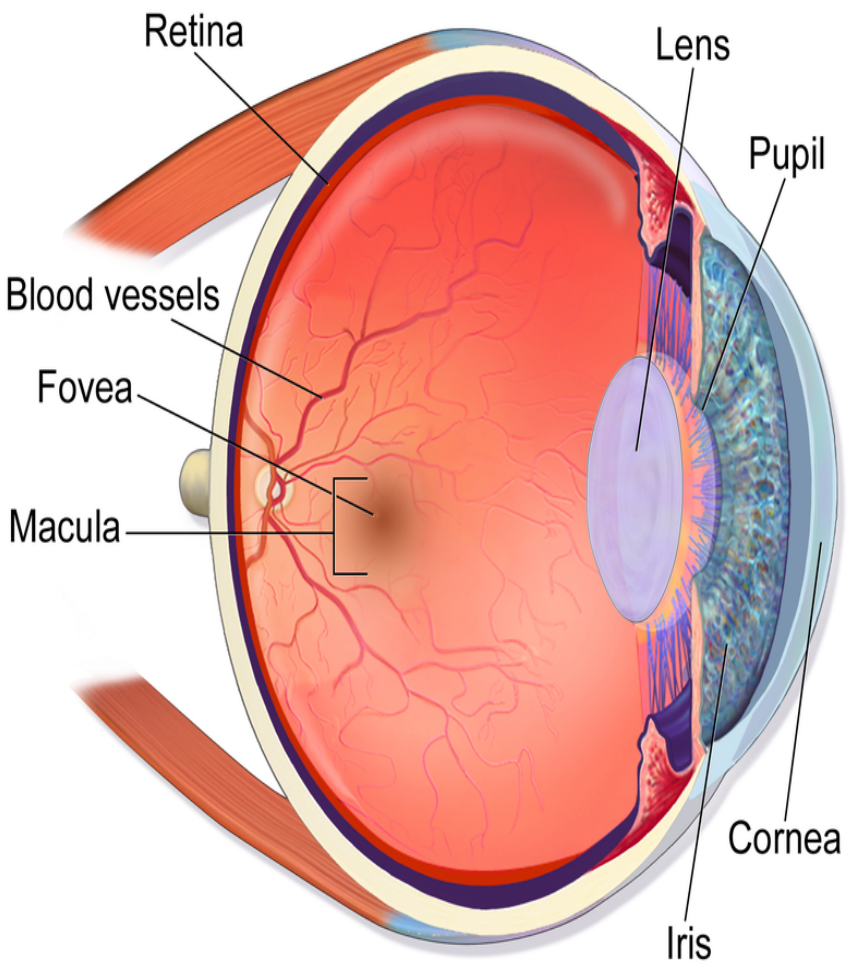
Classify drugs used for treatment of disorders of the eye.

Elaborate on autonomic drugs, anti-inflammatory drugs & and drugs used for glaucoma

Outline ocular toxicity of some drugs

# Anatomy of the Eye



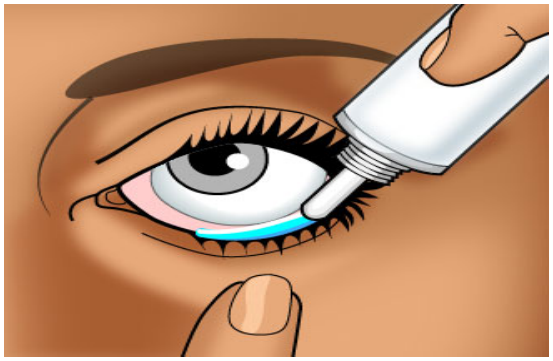




Eye Anatomy

# How drugs can be delivered to ocular tissue?

## Locally (Topically): more common

- Eye drops
- Ointments
- Injections
  - Periocular injection
  - Intraocular injection



## Systemically:

- Orally
- IV

## Eye drops

- Eye drops- most common
- one drop = 50 µl
- Their contract time is low to **be used several times**

## Ointment

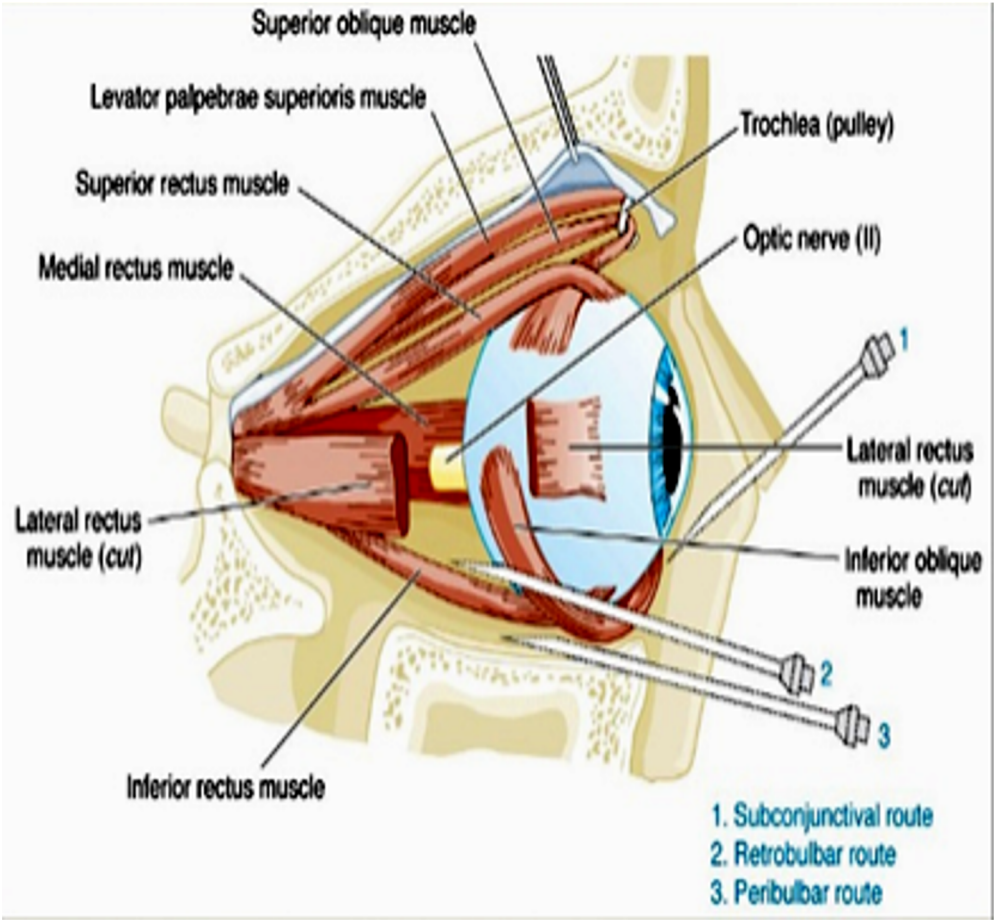
**Increase the contact time** of ocular medication to ocular surface thus **better effect**

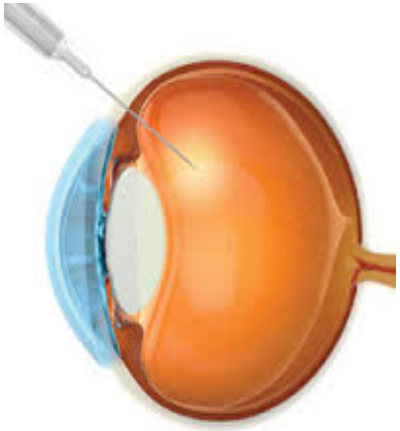
**Disadvantages**

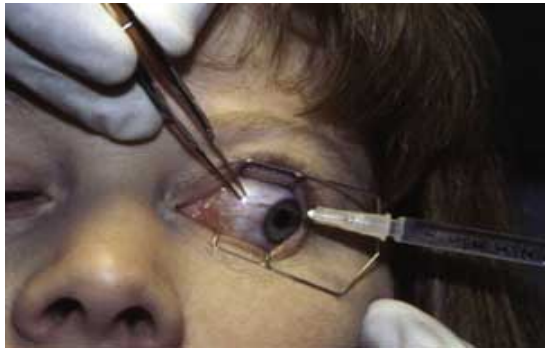
The drug has to be **high lipid soluble** to have the maximum effect

# Peri-ocular injections

- Subconjunctival, retrobulbar or peribulbar
- reach behind iris-lens diaphragm **better than** topical application
- For infection of anterior segment and inflammation of uvea
- bypass the conjunctival and corneal epithelium which is good for **drugs with low lipid solubility (e.g. penicillins)**
- **Steroid and local anesthetics** can be applied this way





https://www.youtube.com/watch?v=3JuQGUovUGU

# Intraocular injections

Intracameral or intravitreal

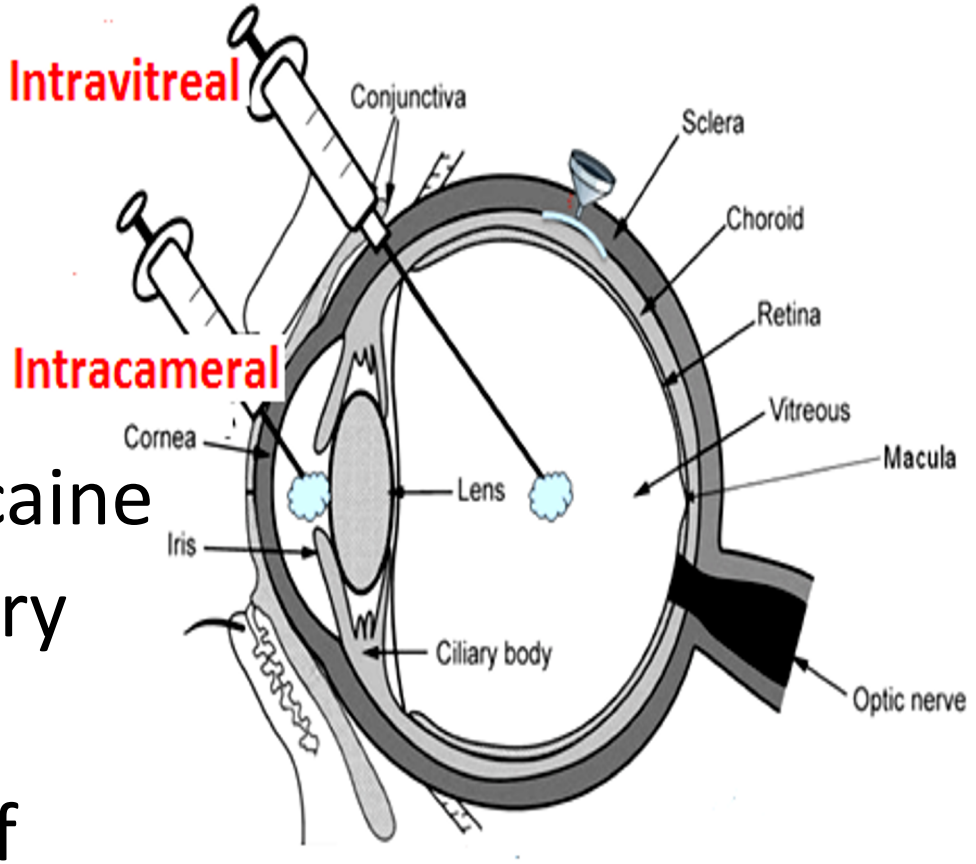
E.g.

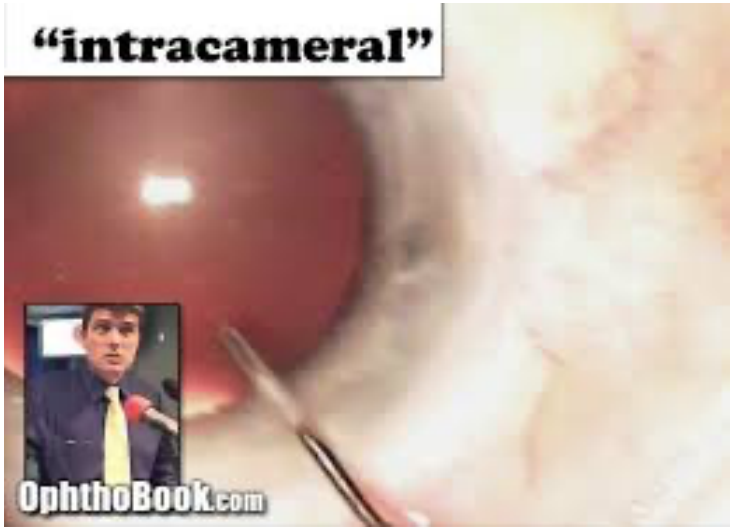
- **Intracameral**

  acetylcholine or lidocaine during cataract surgery
- **Intravitreal**

  Antibiotics in cases of endophthalmitis
- **Intravitreal**

  steroid in macular edema



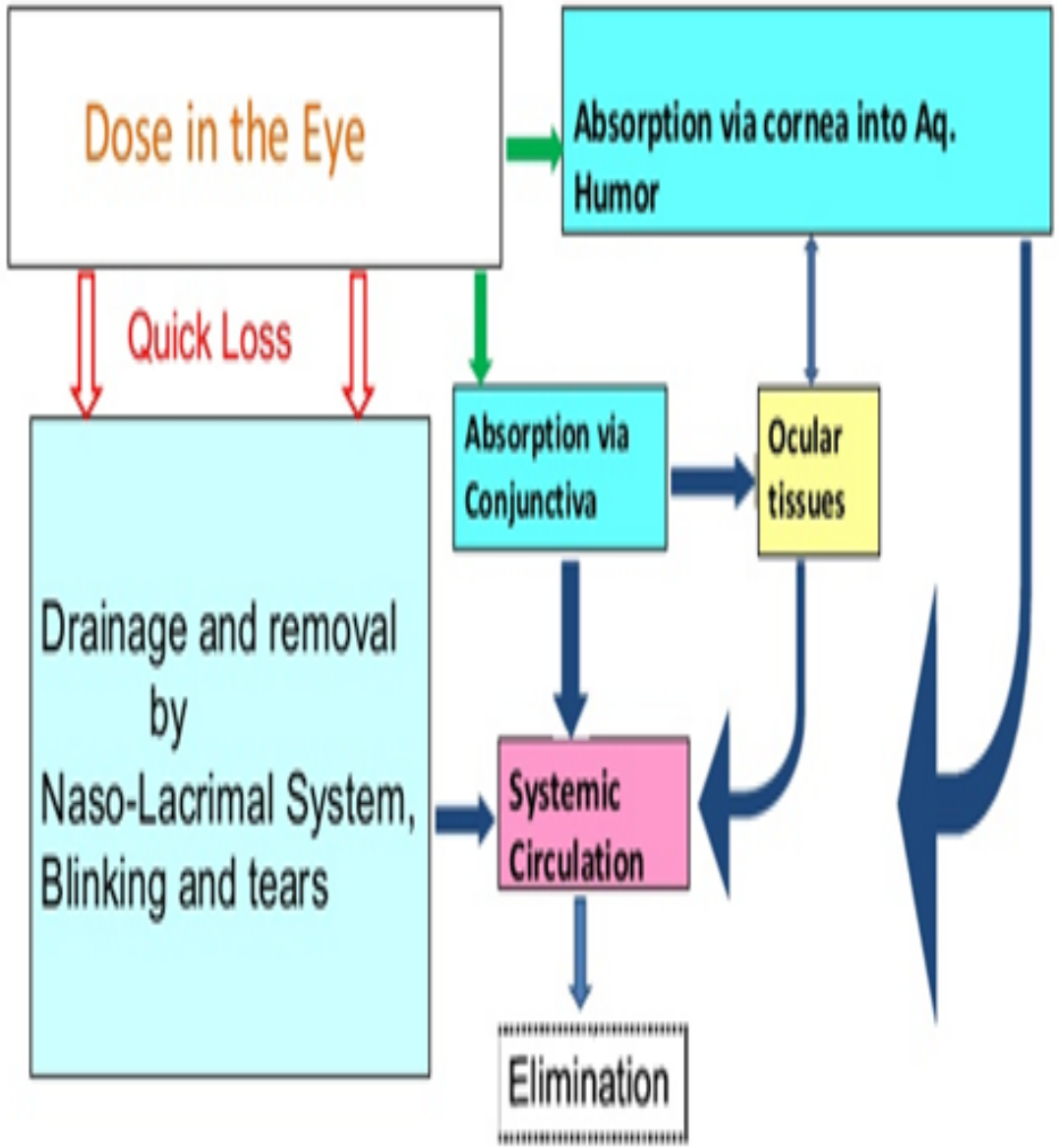

https://www.youtube.com/watch?v=HRM9LaPnbUw

# TOPICAL DRUGS

**Rate of absorption is determined:**

- **Drug residence time**: can be Prolonged by change of formulation.

- **Metabolism** esterases
- **Elimination** by nasolacrimal drainage.
- **Diffusion** across cornea & conjunctiva.



# SYSTEMIC DRUGS

## Oral or IV

- Factors that can control systemic drug penetration into ocular tissue are:
  - **lipid solubility of the drug**: more penetration with high lipid solubility
  - **Protein binding:** more effect with low protein binding
  - **Eye inflammation:** more penetration with ocular inflammation

# OCULAR DRUGS

**Autonomic drugs**

Miotics
Mydriatics
Cycloplegics

**Antiglaucoma Drugs**

**Anti-inflammatory drugs**

Steroids & NSAIDs

**Chemotherapeutics**

Antibacterial,
Antifungal,
Antiviral

**Local anesthetics**

**Ocular lubricants**

# AUTONOMIC DRUGS ACTING ON THE EYE

## PARASYMPATHETIC DRUGS

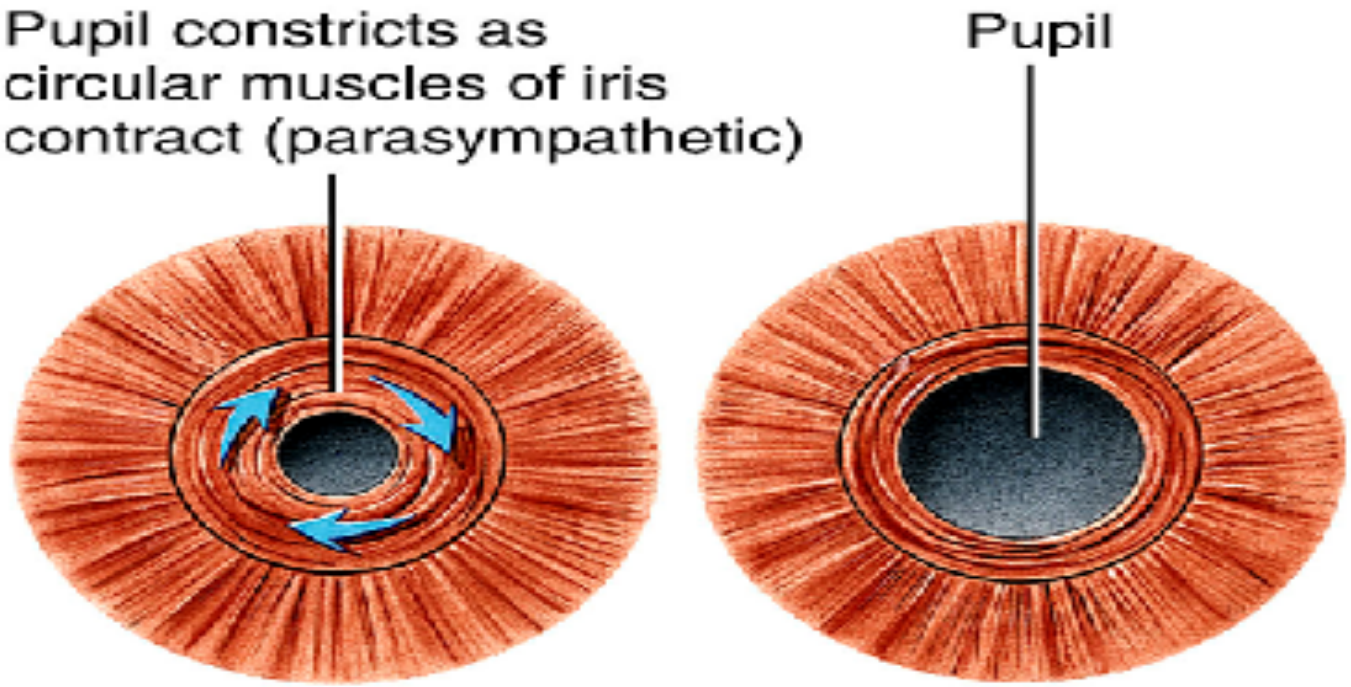
### Cholinergic drugs

- **Direct agonists**
  - Carbachol, methacholine, pilocarpine
- **Indirect acting agonists (anticholinesterases)**
  - **Reversible** :Physostigmine, demecarium
  - **Irreversible**: Ecothiophate, Isoflurophate

# Ocular actions of cholinergic drugs

- Constriction of the pupillary sphincter muscle **(miosis)**
- Contraction of the ciliary muscle **(accommodation for near vision).**
- Decrease in intraocular pressure **↓ IOP.**
- increases aqueous outflow through the trabecular meshwork into canal of Schlemm by ciliary muscle contraction.
- Increased lacrimation
- Conjunctival Vasodilatation

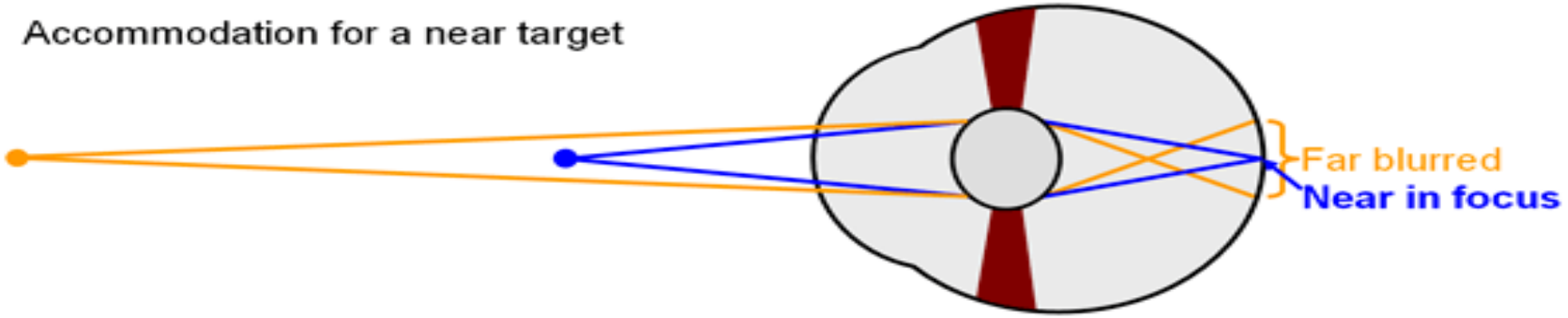
# Pupillary Muscles

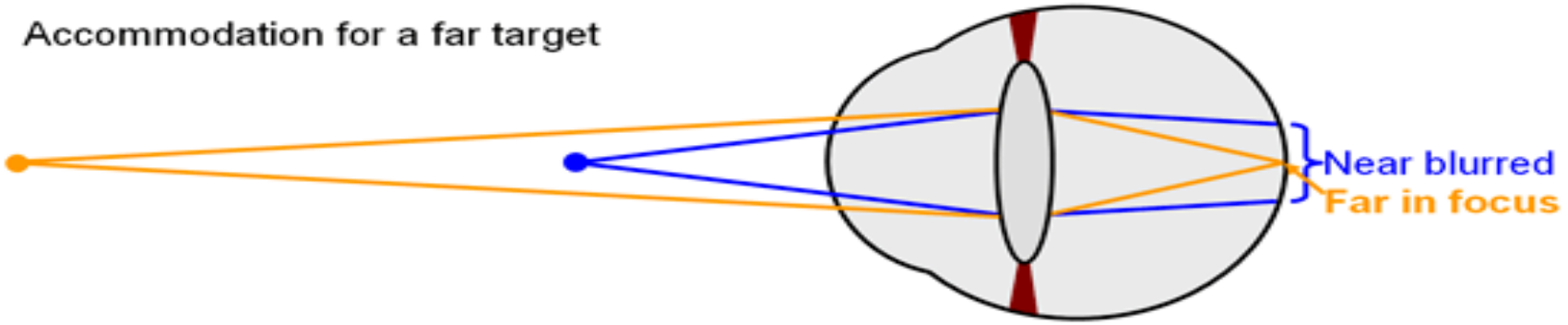



**Miosis by parasympathetic drugs**

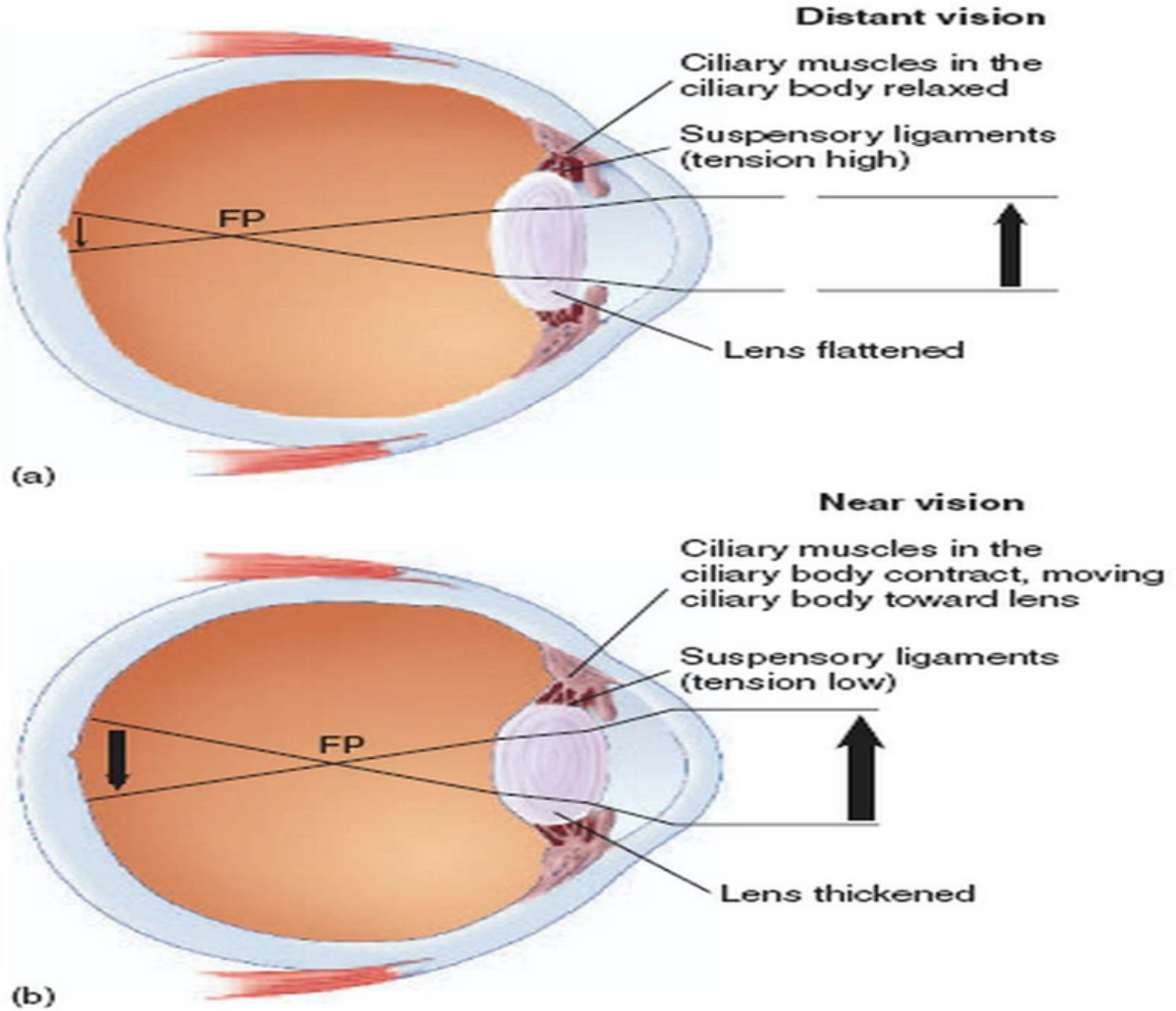
# Accommodation For near vision by Parasympathetic drugs

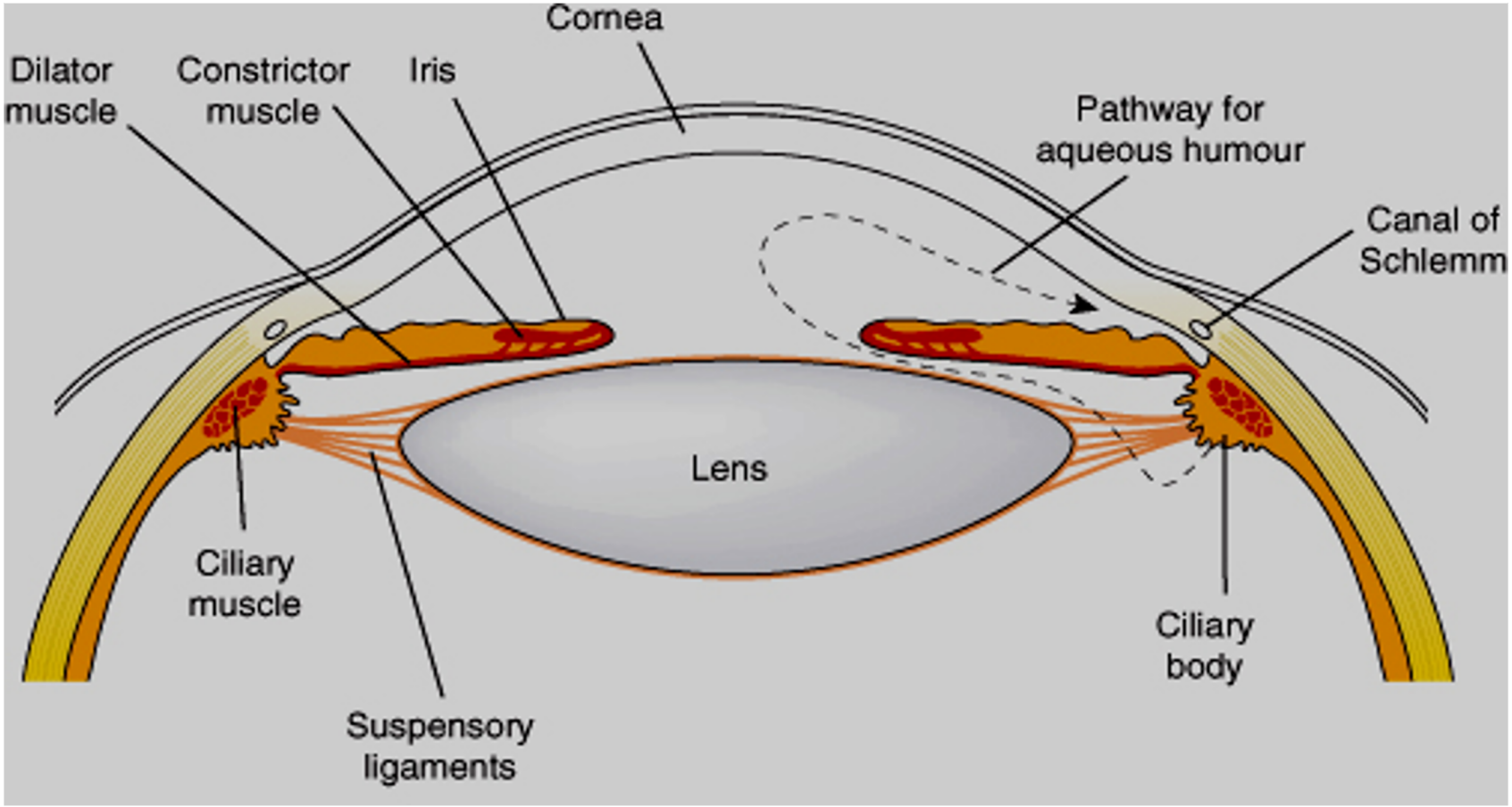
| | Near vision | Far vision |
|---|---|---|
| Ciliary muscles | Contraction | relaxation |
| Suspensory ligaments | relaxation | contraction |
| Lens | Thick, more convex | Thin, flattened |



# Accommodation For near vision by Parasympathetic drugs



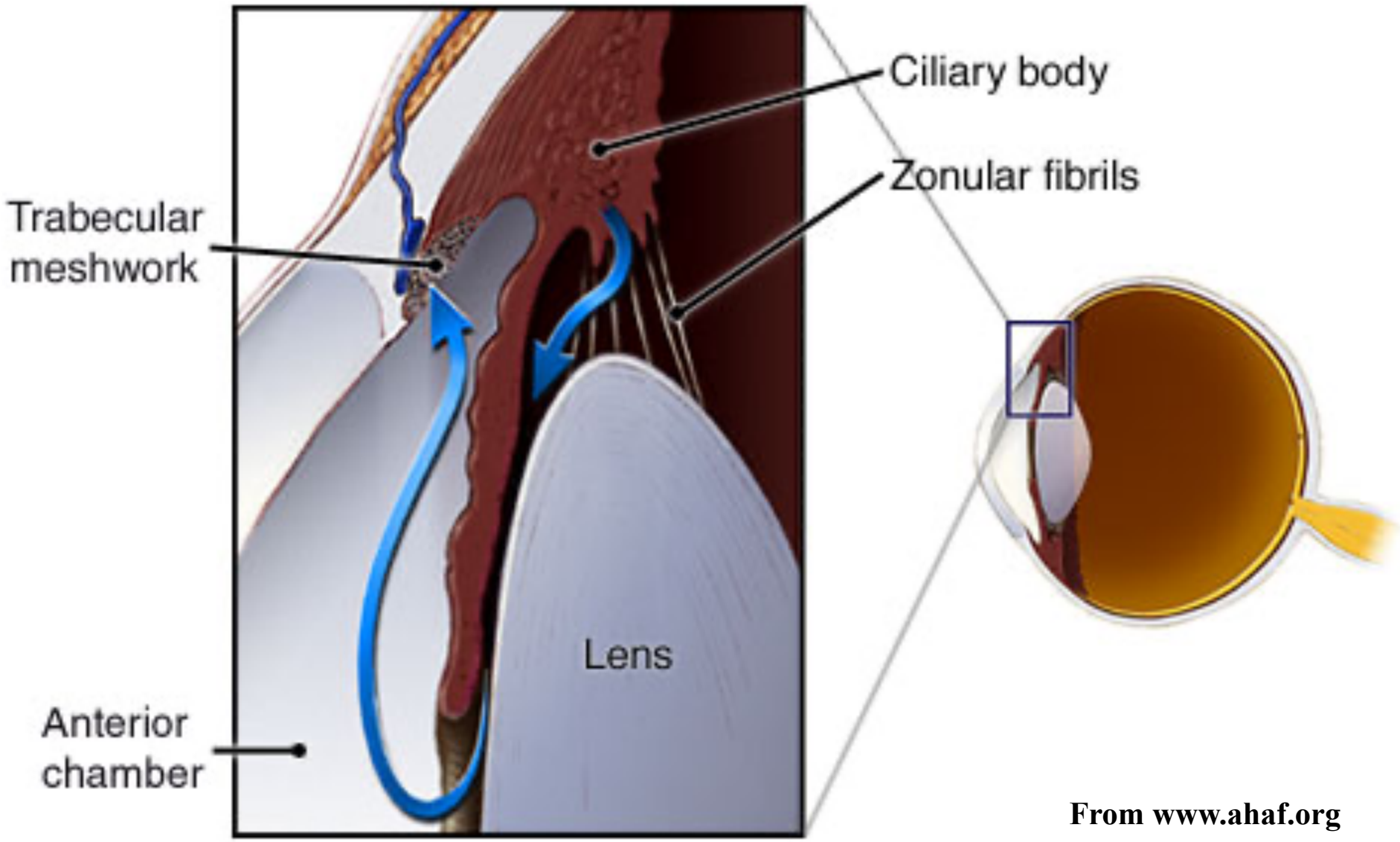



The aqueous humor is secreted by the epithelium of ciliary body. Produced by a combination of active transport of ions and ultrafiltration of interstitial fluid. The fluid flows over the surface of the lens, out through the pupil into the anterior chamber. Flows through the trabecular meshwork into Schlemm's canal and is collected in the scleral veins.

# Decrease in IOP by parasympathetic drugs

# Flow of Aqueous Humor:

## A Closer Look at the Trabecular Meshwork




From www.ahaf.org

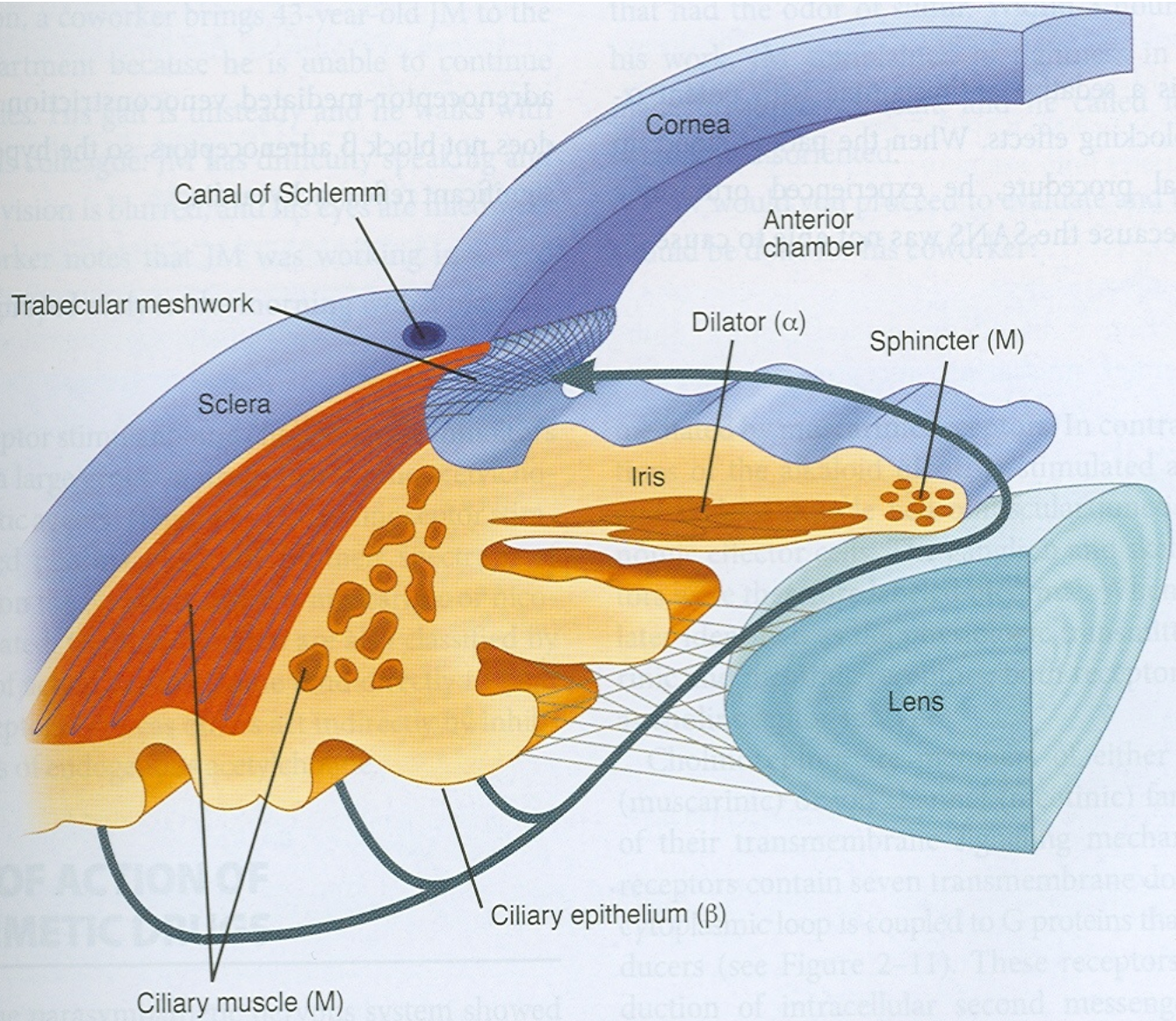



**FIGURE 6–9** Structures of the anterior chamber of the eye. Tissues with significant autonomic functions and the associated ANS receptors are shown in this schematic diagram. Aqueous humor is secreted by the epithelium of the ciliary body, flows into the space in front of the iris, flows through the trabecular meshwork, and exits via the canal of Schlemm (*arrow*). Blockade of the β adrenoceptors associated with the ciliary epithelium causes decreased secretion of aqueous. Blood vessels (not shown) in the sclera are also under autonomic control and influence aqueous drainage.

# Uses of Cholinergic drugs

- Glaucoma (open and closed angle)
- Counteract action of mydriatics
- To break iris-lens adhesions
- in accommodative esotropia **(ecothiophate)**

## Ocular adverse effects

Diminished vision (myopia), headache

# Uses of Cholinergic drugs

| Drugs | Ocular uses |
| --- | --- |
| Carbachol<br>Methacholine | Induction of miosis in surgery<br>Open angle glaucoma |
| Pilocarpine | In open angle glaucoma |
| Physostigmine<br>Ecothiophate<br>Isoflurophate | Glaucoma, accommodative esotropia |

# Cholinergic (Muscarininc) antagonists

| Drugs | Duration of effect |
|---|---|
| **Natural alkaloids**<br>▪ Atropine<br>▪ Scopolamine (hyoscine) | <br>7-10 days<br>3-7 days |
| **Synthetic atropine substitutes**<br>▪ Homatropine<br>▪ Cyclopentolate<br>▪ Tropicamide | 1-3 days<br>24 hour<br>6 hour |

# Cholinergic (Muscarininc) antagonists

- **Passive Mydriasis :** *due to relaxation of circular muscles*
- **Cycloplegia (loss of near accommodation)**

  due to relaxation of ciliary muscles
- Loss of light reflex.
- increased I.O.P # glaucoma.
- ↓ Lacrimal secretion → sandy eye

# Clinical Uses of cholinergic antagonists:

- Funduscopic examination
- To prevent adhesion in uveitis & iritis
- Measurement of refractive error

# SYMPATHETIC DRUGS

## Adrenergic agonists

**Non-selective agonists ($\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$)**

e.g. epinephrine, dipivefrin (pro-drug of epinephrine)

**Selective agonists (α1)** e.g. phenylephrine

**Selective agonists (α2)** e.g. apraclonidine

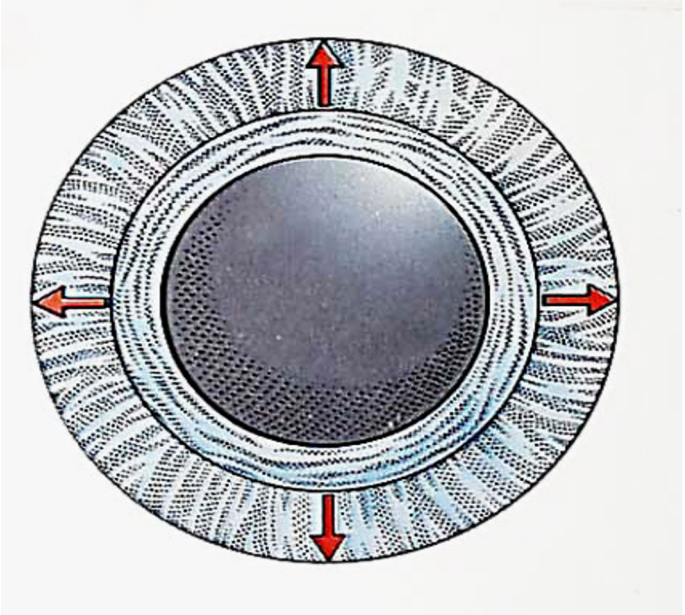
**Non Selective β blockers** e.g. timolol, carteolol

**Selective β1 blocker** betaxolol

# Ocular actions of adrenergic drugs

- Contraction of dilator Pupillae **(Active mydriasis)** **α1**
- Relaxation of ciliary muscles **β2**
- **Vasoconstriction** of conjunctival blood vessels **α1**
- α & β receptors in the blood vessels of the ciliary processes →help in regulation of aqueous humour formation.

**Mydriasis**



| Eye | Parasympathetic drugs | Sympathetic drugs |
|---|---|---|
| **Iris**<br>**radial muscle**<br>**circular muscle** | No effect<br>Contraction (miosis)<br>M3 | Contraction (Mydriasis) α1<br>No effect |
| **Ciliary muscle** | Contraction M3 | Relaxation β2 |
| **Accommodation** | for near vision | for far vision |
| **Conjunctival blood vessels** | Conjunctival Vasodilatation and congestion of blood vessels | Conjunctival Vasoconstriction and decongestion of blood vessels |

# SYMPATHETIC DRUGS

## Adrenergic agonists

### Non-selective agonists ($\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$)

- e.g. epinephrine, dipivefrin (pro-drug of epinephrine)
- Used locally as eye drops
- In open angle glaucoma

**Mechanism:** ↑ uveoscleral outflow of aqueous humor

**Side Effects**: headache, arrhythmia, elevated BP

**C/I :** in patients with narrow angles as they may precipitate closed angle glaucoma .

# Selective α1 agonists

## e.g. phenylephrine

**Active mydriasis** due to contraction of radial muscles of the eye **(without cycloplegia)**

**Used in:**

- Funduscopic examination of the eye
- To prevent adhesion in uveitis & iritis
- Decongestant in minor allergic hyperemia of eye.

**Side effects:**

- May cause significant increase in blood pressure
- Rebound congestion
- precipitation of acute angle-closure glaucoma in patients with narrow angles.

# Selective α2 agonists

## e.g. apraclonidine (eye drops)

**Mechanism:**

↓ production of aqueous humor, and

↑ uveoscleral outflow of aqueous humor

**Uses:**

Open glaucoma treatment

Prophylaxis against IOP Spiking after glaucoma laser procedures.

**Side Effects:**

Headache, bradycardia, hypotension.

# β blockers

- **Non-selective:** timolol, carteolol
- **Selective $\beta_1$** : betaxolol "cardioselective"
- Given topically as eye drops

**Mechanism:**

Act on ciliary body to ↓ production of aqueous humor.

**Uses:** open angle glaucoma

**Advantages** can be used in patients with hypertension

**Side effects**

- **Ocular effects:** irritation

# Treatment of open angle glaucoma (chronic)

The main goal is to decrease IOP by:

- Decreasing production of aqueous humor
  - Beta blockers
  - Alpha-2 agonists
  - Carbonic anhydrase inhibitors
- Increasing outflow of aqueous humor
  - Prostaglandins
  - Adrenergic agonists, nonspecific
  - Parasympathomimetics

Prostaglandins and β blockers are the most popular

## Carbonic anhydrase inhibitors

e.g. acetazolamide (oral), dorzolamide (topical)

Mechanism: ↓ production of aqueous humor by blocking carbonic anhydrase enzyme required for production of bicarbonate ions (transported to posterior chamber, carrying osmotic water flow).

Side Effects:

Myopia, malaise, anorexia, GI upset, headache
Metabolic acidosis, renal stone

Contraindication:

Sulpha allergy, pregnancy

# Prostaglandin analogues

E.g. latanoprost, travoprost

**Mechanism:** increase uveoscleral aqueous outflow.

**Latanoprost** is preferred due to lesser adverse effects.

They are used topically as eye drops & **once a day.**

**Uses:** open angle glaucoma, replaced beta blockers.

**Side Effects:**

pigmentation of the iris (heterochromia iridis).

# Treatment of narrow closed angle glaucoma (Acute angle glaucoma)

- Acute, painful increases of intraocular pressure due to occlusion of the outflow drainage pathway.
- Emergency situation that require treatment before surgery **(Iridectomy)**

**The use of drugs is limited to :**

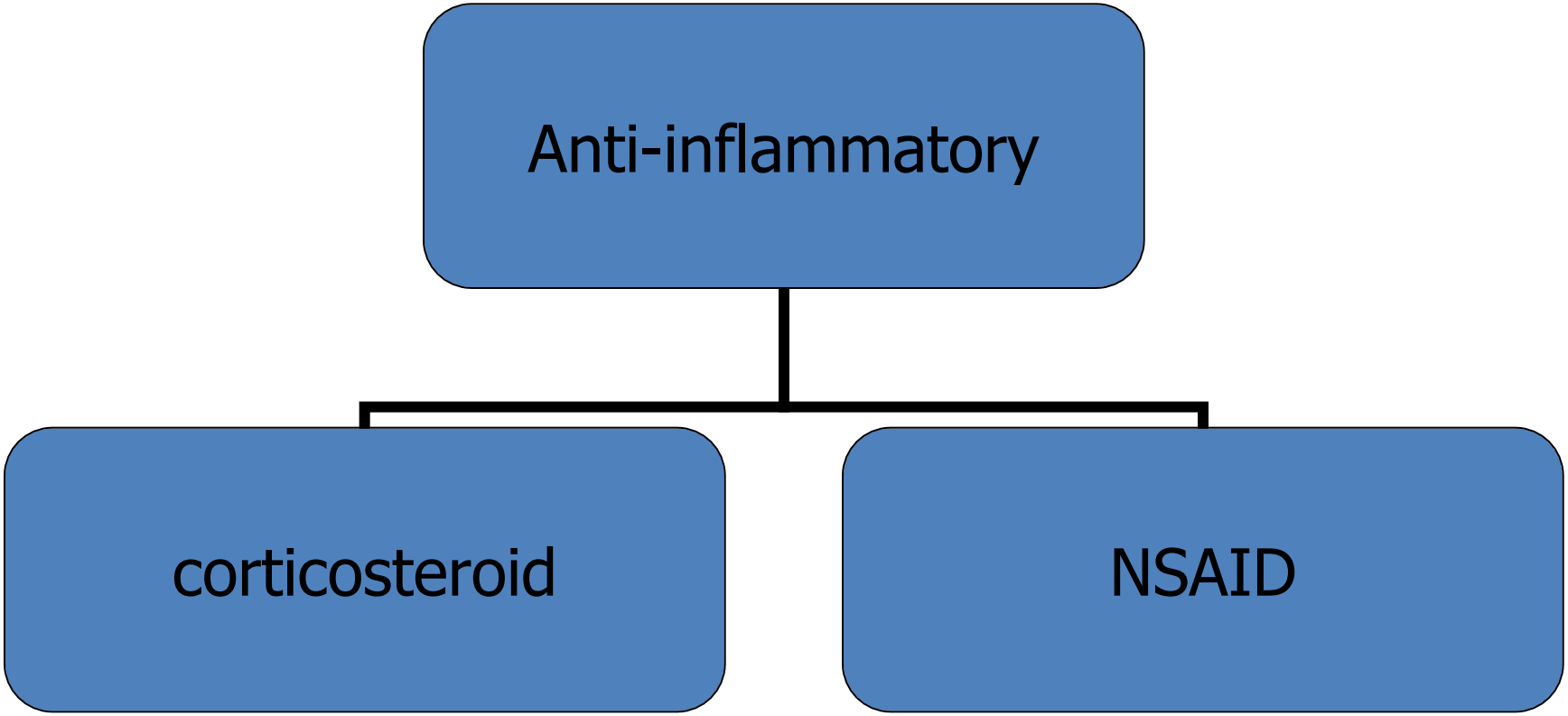
- **Oral Acetazolamide**
- **Topical cholinomimetics** e.g.: pilocarpine
- **Osmotic agents:** hypertonic solutions of ( Mannitol, Glycerol).
- **Analgesics:** pethidine or morphine (for pain)

# Osmotic agents (dehydrating agents)

## Mechanism:

- IV infusion of hypertonic solution (**Mannitol, Glycerol**).
- can **rapidly** lower IOP by decreasing vitreous volume prior to anterior surgical procedures
- **Glycerol 50% syrup**, orally (cause nausea, hyperglycemia).
- **Mannitol 20% IV** (cause fluid overload and not used in heart failure).
- used only in **acute situations** to temporarily reduce high IOP until more definitive treatments can be given.

**Side effects:** Diuresis, circulatory overload, pulmonary edema and heart failure, central nervous system effects such as seizure, and cerebral hemorrhage.


Anti-inflammatory
corticosteroid
NSAID

# Corticosteroids

**Mechanism:** inhibition of arachidonic acid release from phospholipids by inhibiting phosphlipase A2

**Topical**

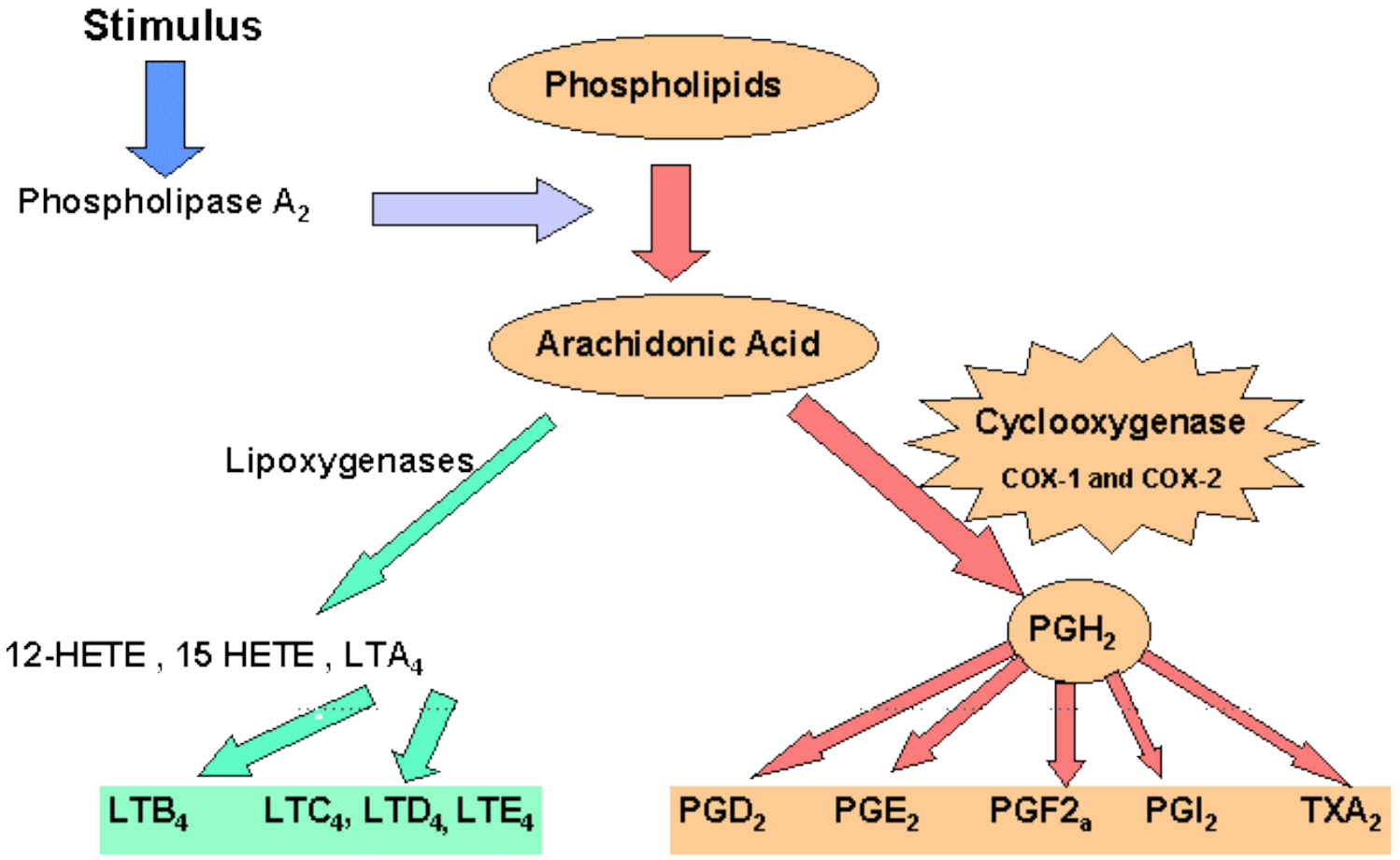
- E.g. prednisolone, dexamethasone, hydrocortisone
- **Uses:** anterior uveitis, severe allergic conjunctivitis, scleritis, prevention and suppression of corneal graft rejection.

**Systemic**

- E.g. prednisolone, cortisone
- **Uses:** posterior uveitis, optic neuritis

**Ocular ADRS:** Glaucoma, increase IOP, cataract, skin atrophy, secondary infection, delayed wound healing.

Figure 2 : Biosynthesis of eicosanoids



# NSAID

- **E.g. ketorolac, diclofenac, Flurbiprofen**

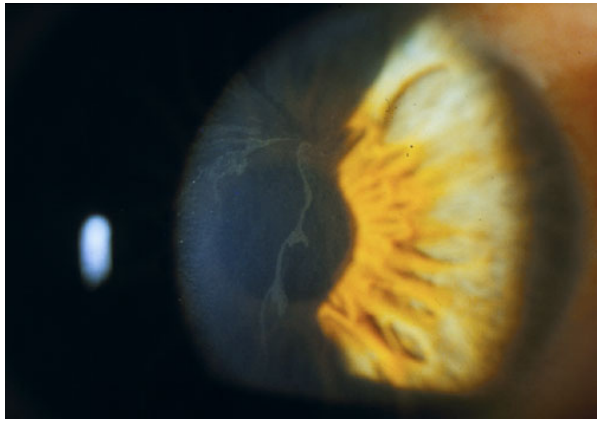
**Mechanism:** inhibition of cyclo-oxygenase

**Uses:**

- **Flurbiprofen** pre-operatively to prevent miosis during cataract surgery.
- **Diclofenac:** postoperatively, mild allergic conjunctivitis, mild uveitis
- **Ketorolac:** cystoid macular edema occurring after cataract surgery

**Side effects:** stinging

# Drugs causing corneal deposits



**Amiodarone & chloroquine :**

- Causes optic neuropathy
- Pigmented deposits of the cornea

**Digitalis** : cardiac failure drug
ocular disturbances & **chromatopsia** with overdose.
**(objects appear yellow**).

**Phenothizines**

cause brown pigmentary deposits in the cornea, conjunctiva & eyelid

**Steroids →** cataract formation, elevated IOP & glaucoma

**Ethambutol** → optic neuropathy characterized by gradual progressive vision loss.

**Sildenafil** → Causes a bluish haze & causing light sensitivity