PHARMACOLOGY OF DRUGS ACTING ON THE EYE

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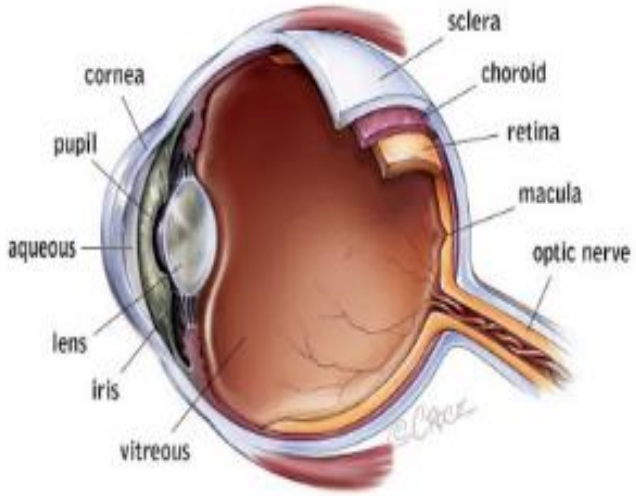
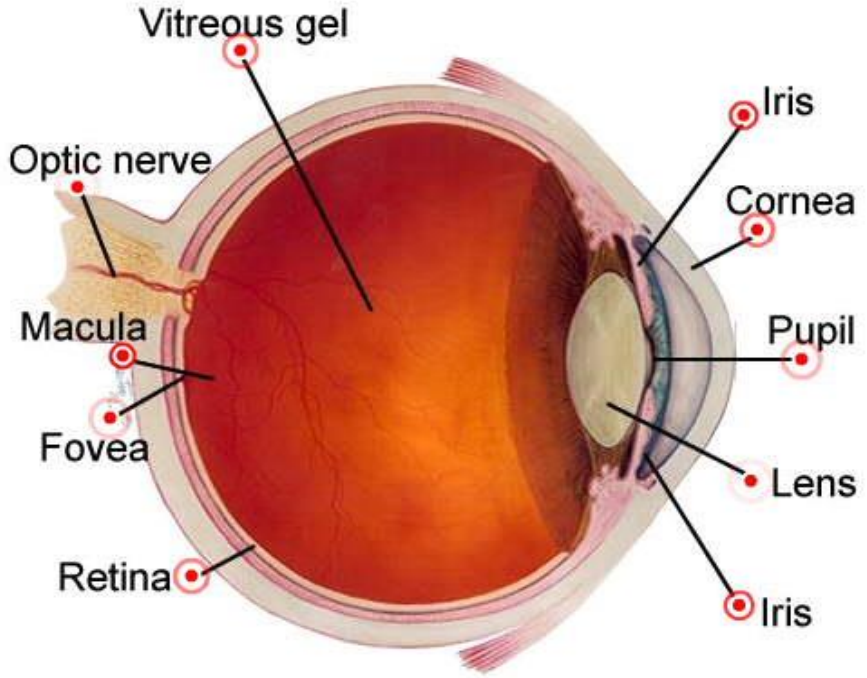




ILOS

Outline common routes of administration of drugs to the eye.

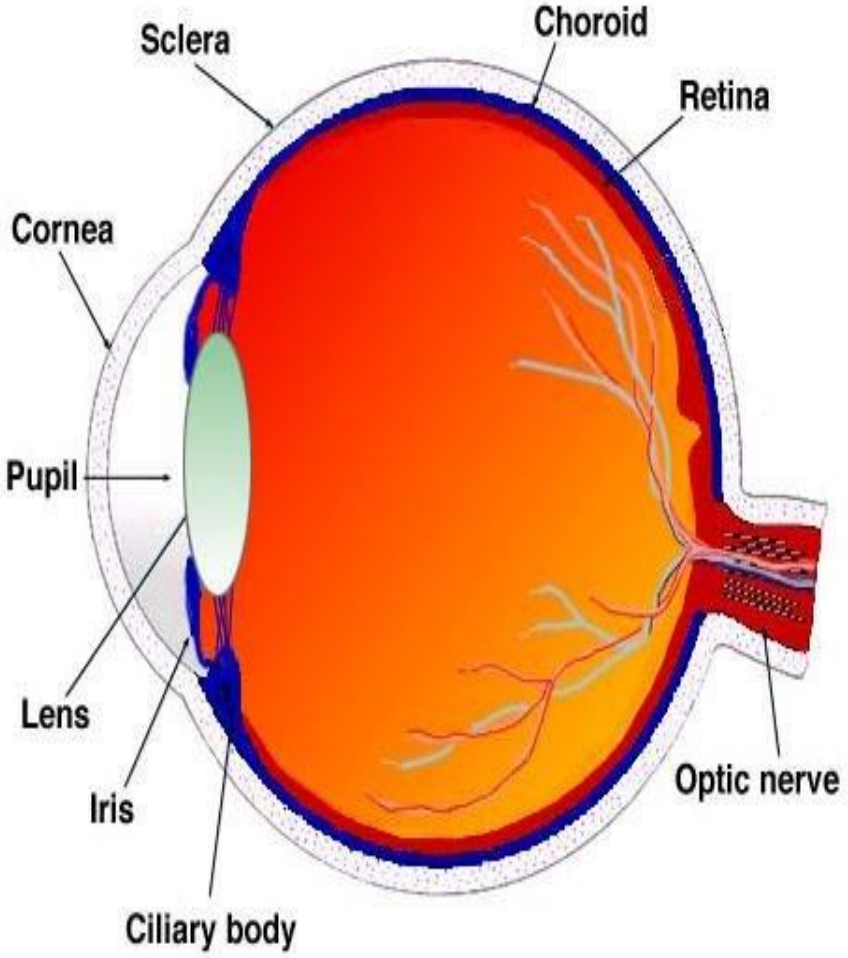
Discuss the pharmacokinetics of drugs applied topically to the eye.

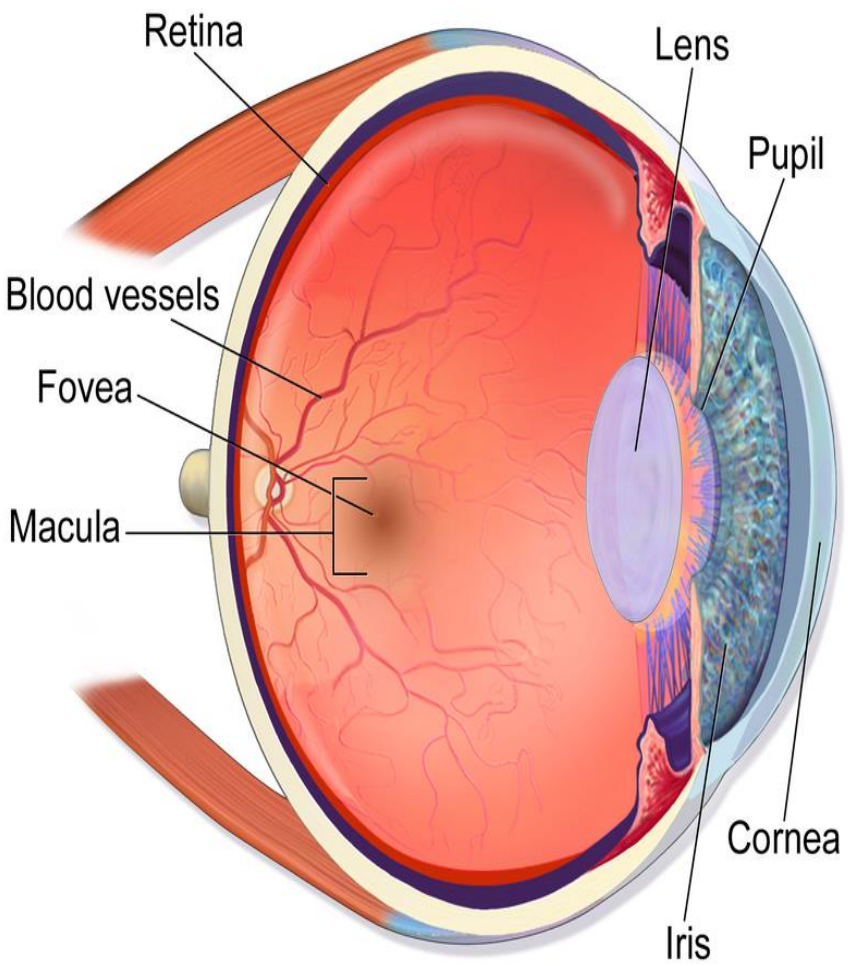
Classify drugs used for treatment of disorders of the eye.

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

Outline ocular toxicity of some drugs

Anatomy of the Eye



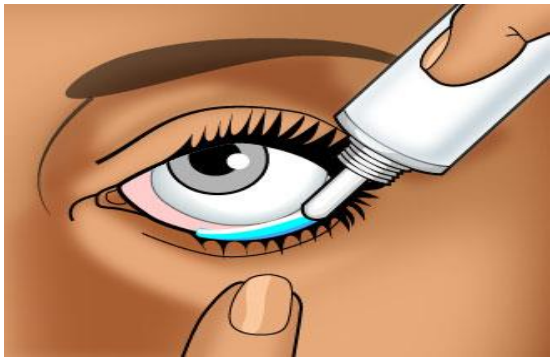


Eye Anatomy

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

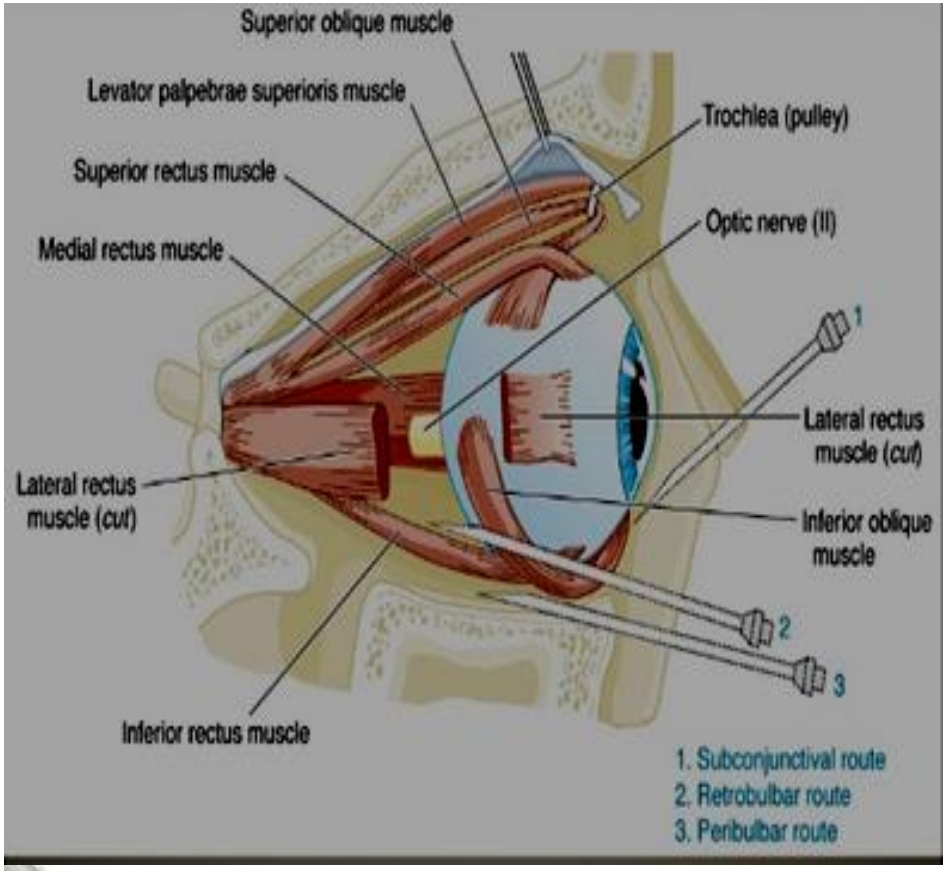
Increase the contact time of ocular medication to ocular surface thus **better effect**

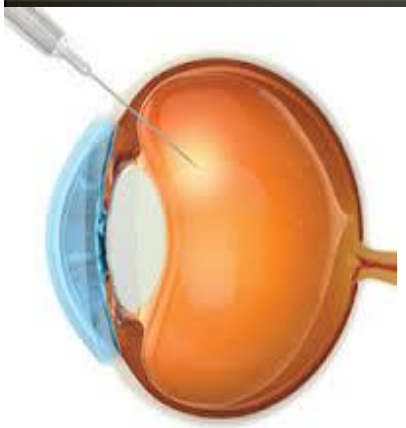
Disadvantages

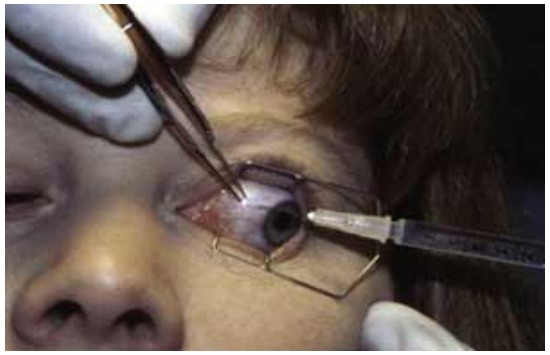
The drug has to be **high lipid soluble** to have the maximum effect

Peri-ocular injections

- Subconjunctival, retrobulbar or peribulbar
- reach behind iris-lens diaphragm **better than** topical application
- 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
- For infection of anterior segment and inflammation of uvea

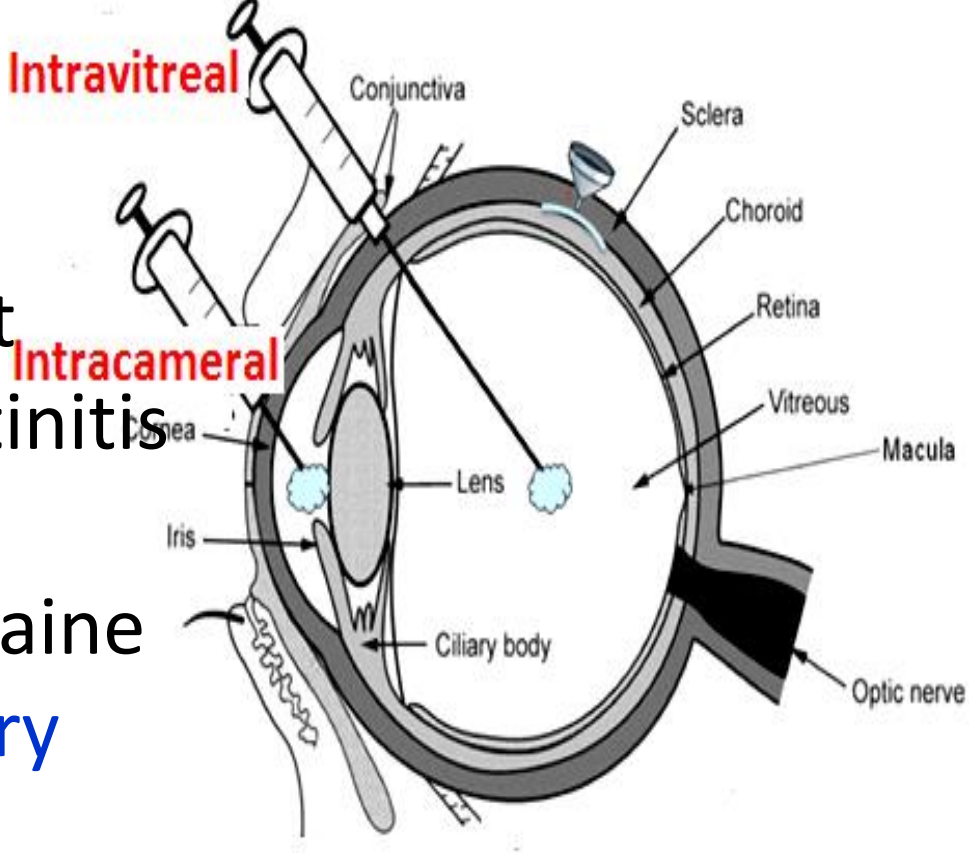






https://www.youtube.com/watch?v=3JuQGUovUGU

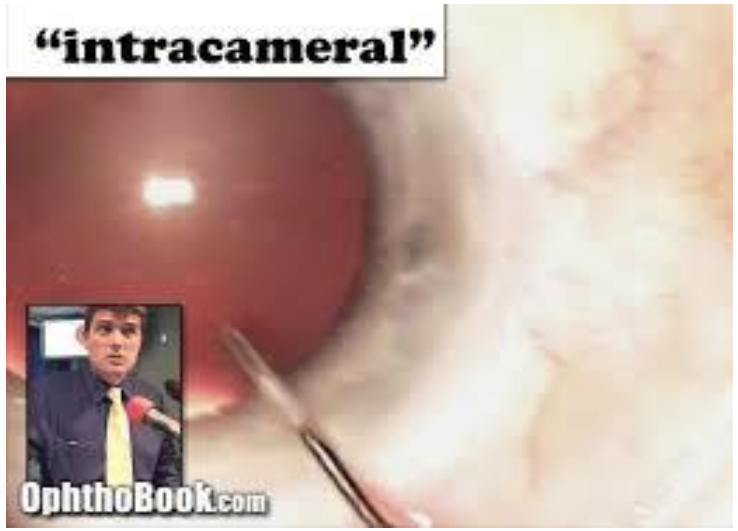
Intraocular injections



Intracameral or intravitreal

Used for anterior segment surgery, infections and retinitis

- **Intracameral** acetylcholine or lidocaine during cataract surgery
- **Intravitreal** Antibiotics in cases of endophthalmitis
- **Intravitreal** steroid in macular edema



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TOPICAL DRUGS

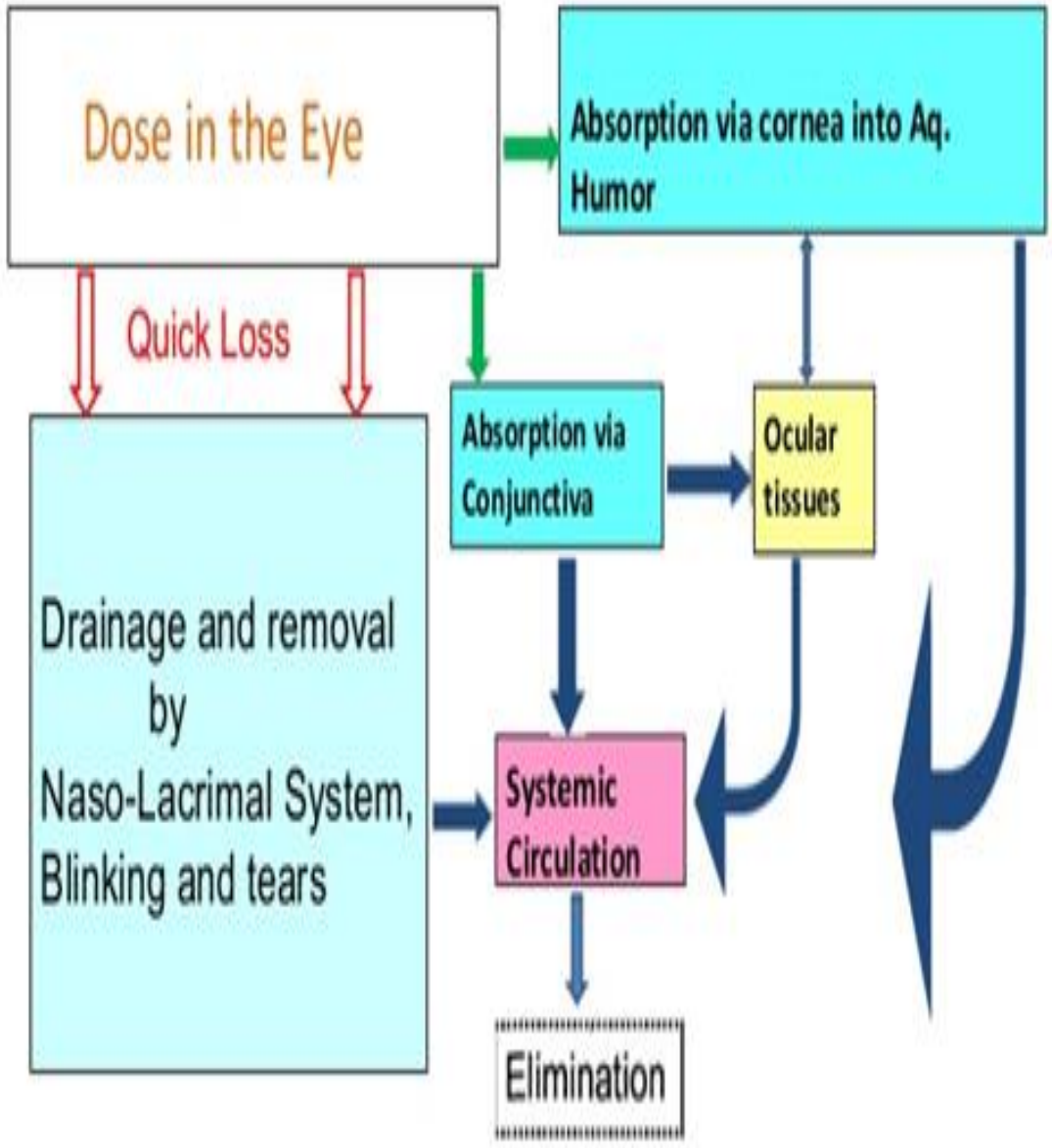
Rate of absorption is determined:

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

- **Metabolism**
  esterases

Esterases activate pro drugs e.g. dipivefrin → adrenaline, latanoprost →PGF2α

- **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

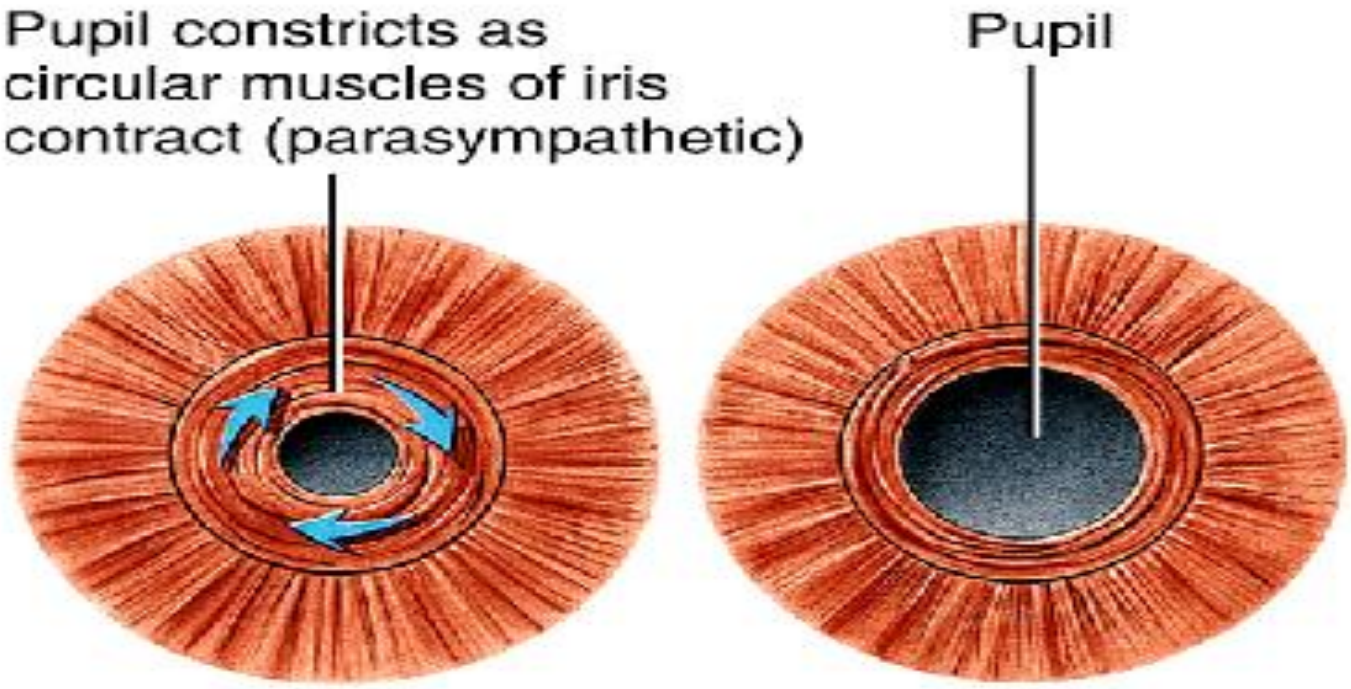
Cholinergic drugs

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

Ocular actions of cholinergic drugs

- Contraction 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

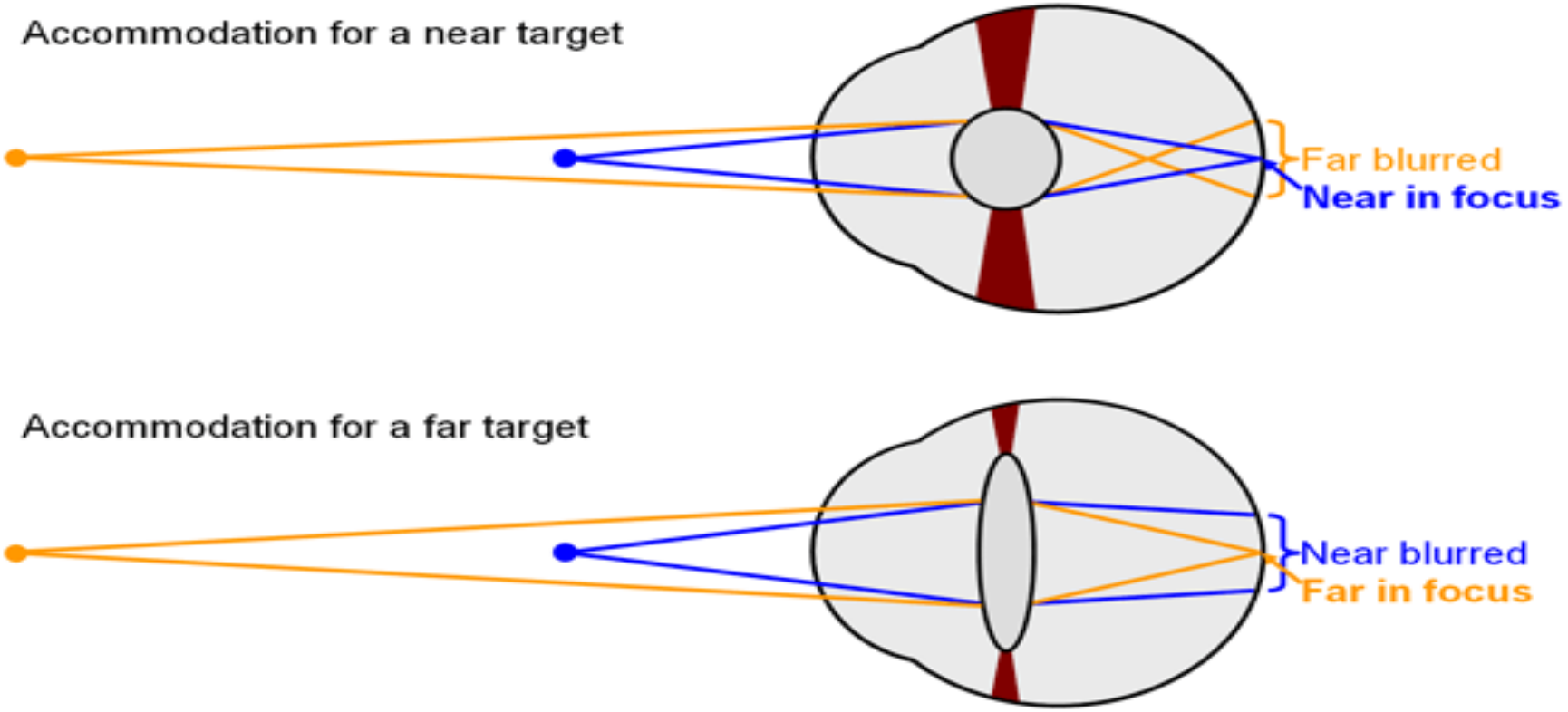
Pupillary Muscles



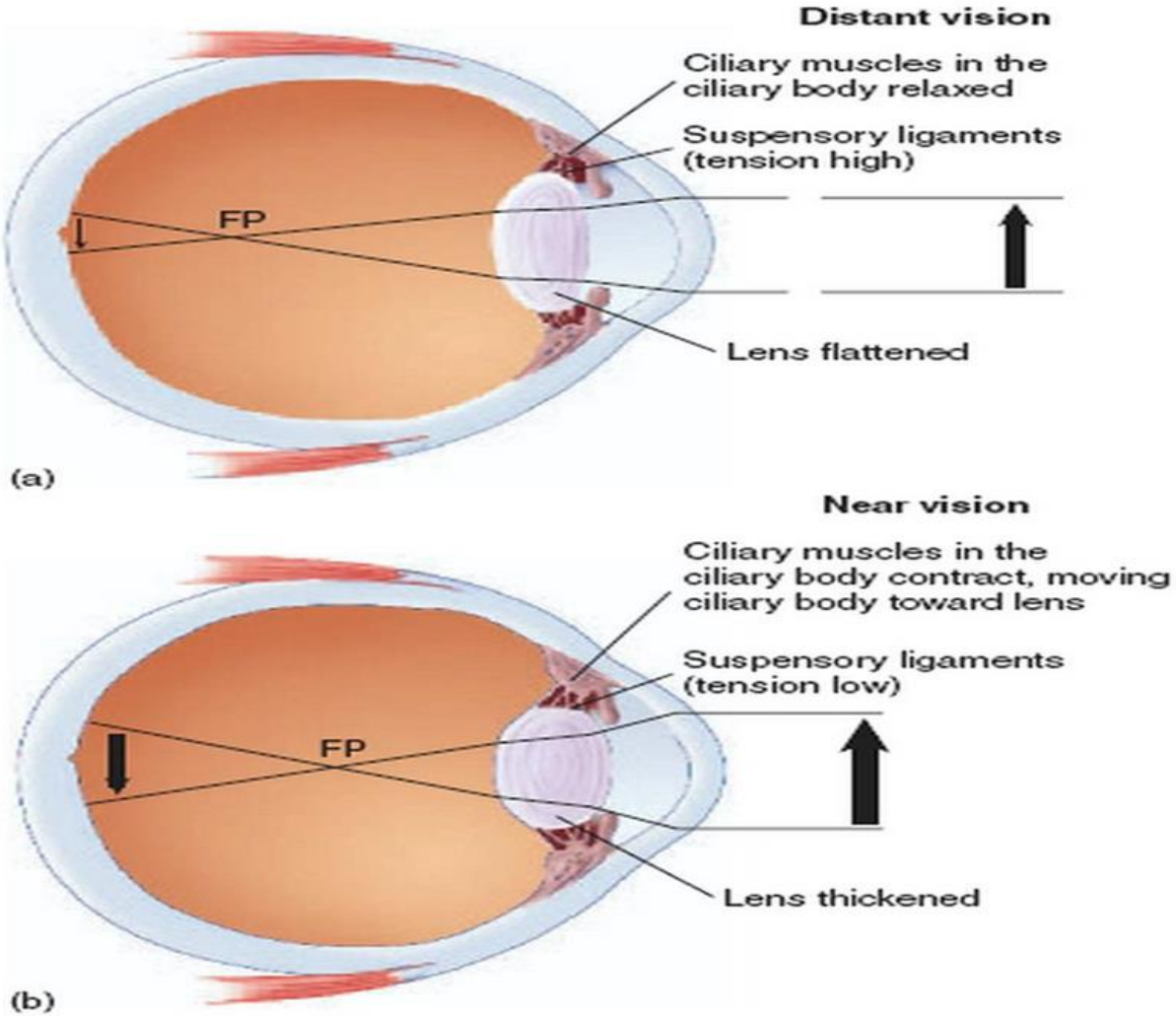
Miosis by parasympathetic drugs

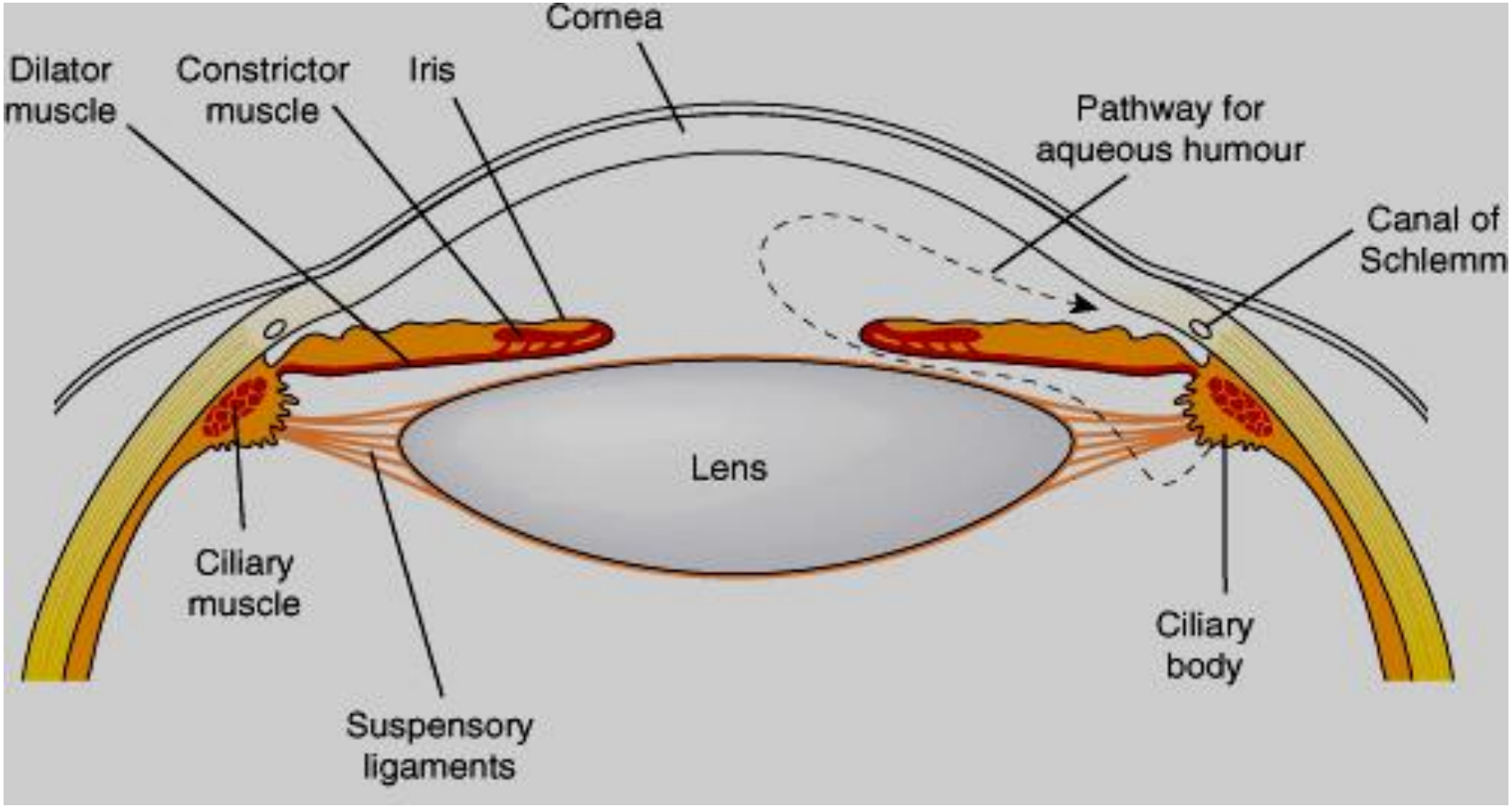
Accommodation For near vision by Parasympathetic drugs

	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. It is 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.

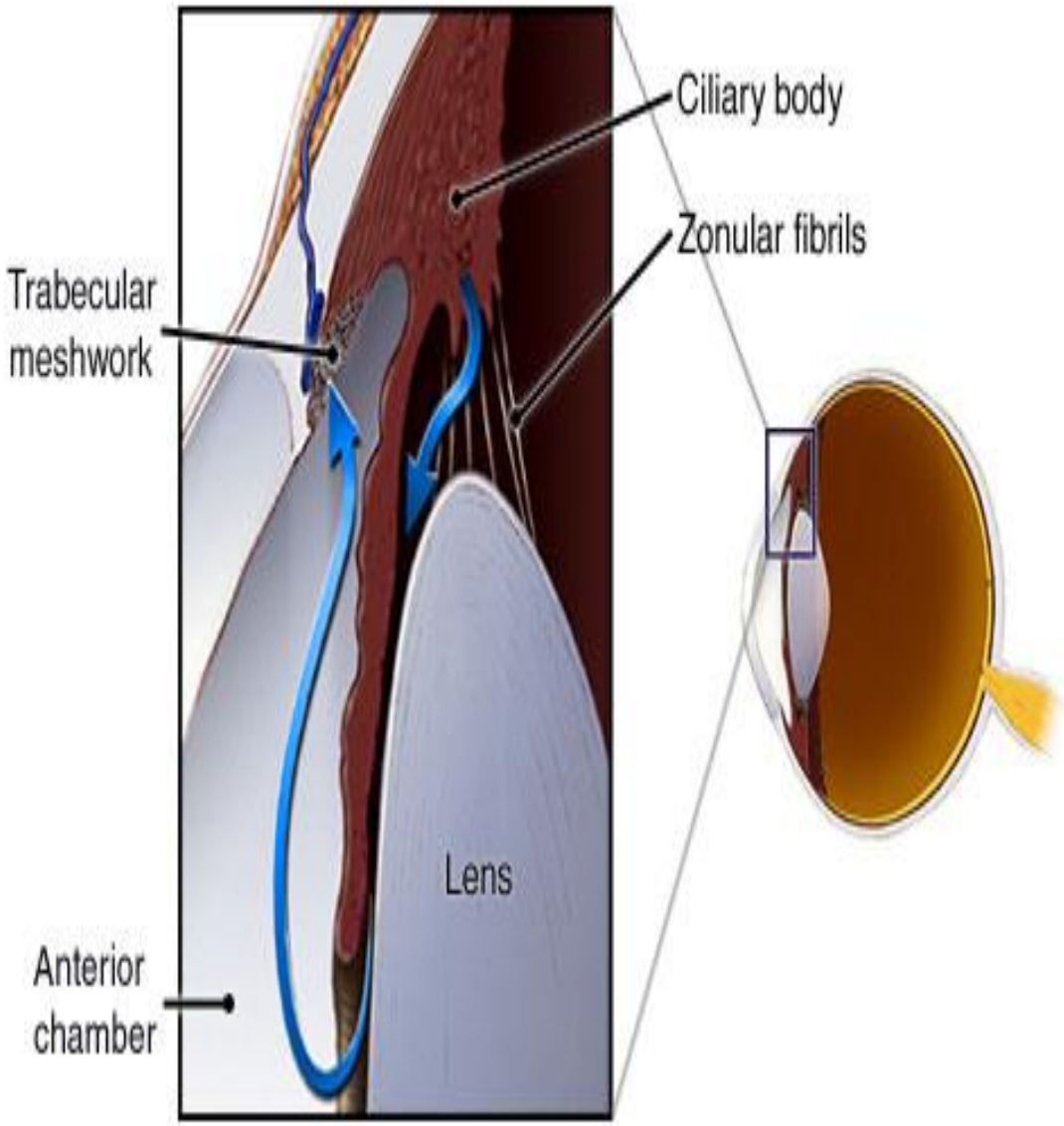
Decrease in IOP by parasympathetic drugs

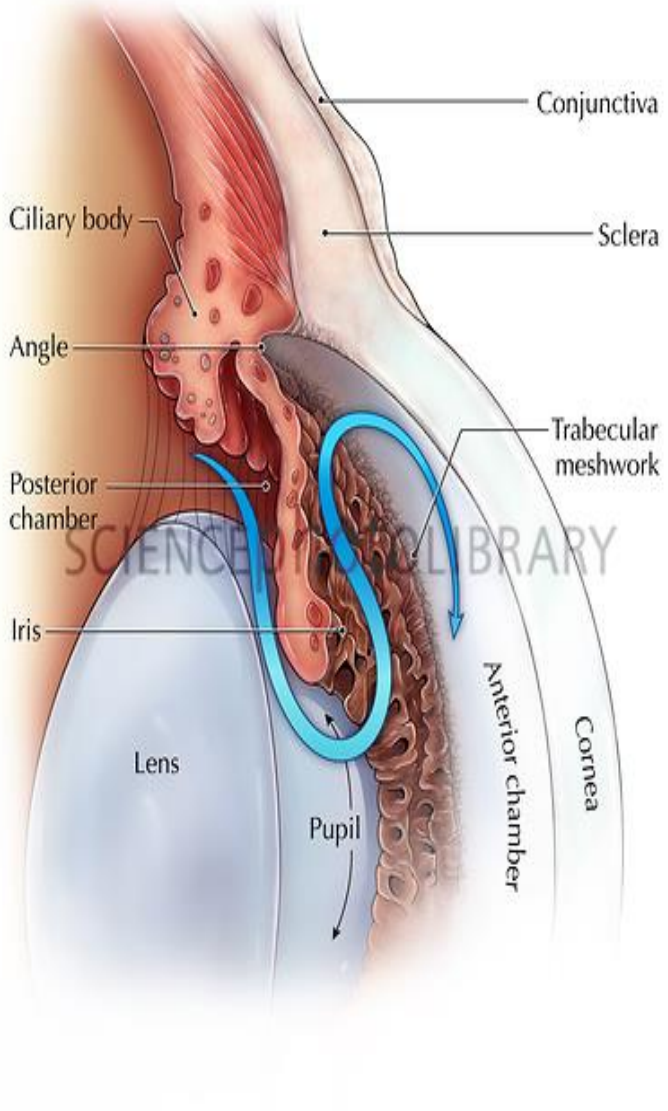
Aqueous production and drainage

- **Production:** The aqueous humor is secreted by the **epithelium of ciliary body**. The fluid flows over the surface of the lens, out through the pupil into the anterior chamber.
- Drainage by
  - the trabecular meshwork into Schlemm's canal.
  - Uveosacral drainage is collected in the scleral veins.

Flow of Aqueous Humor:

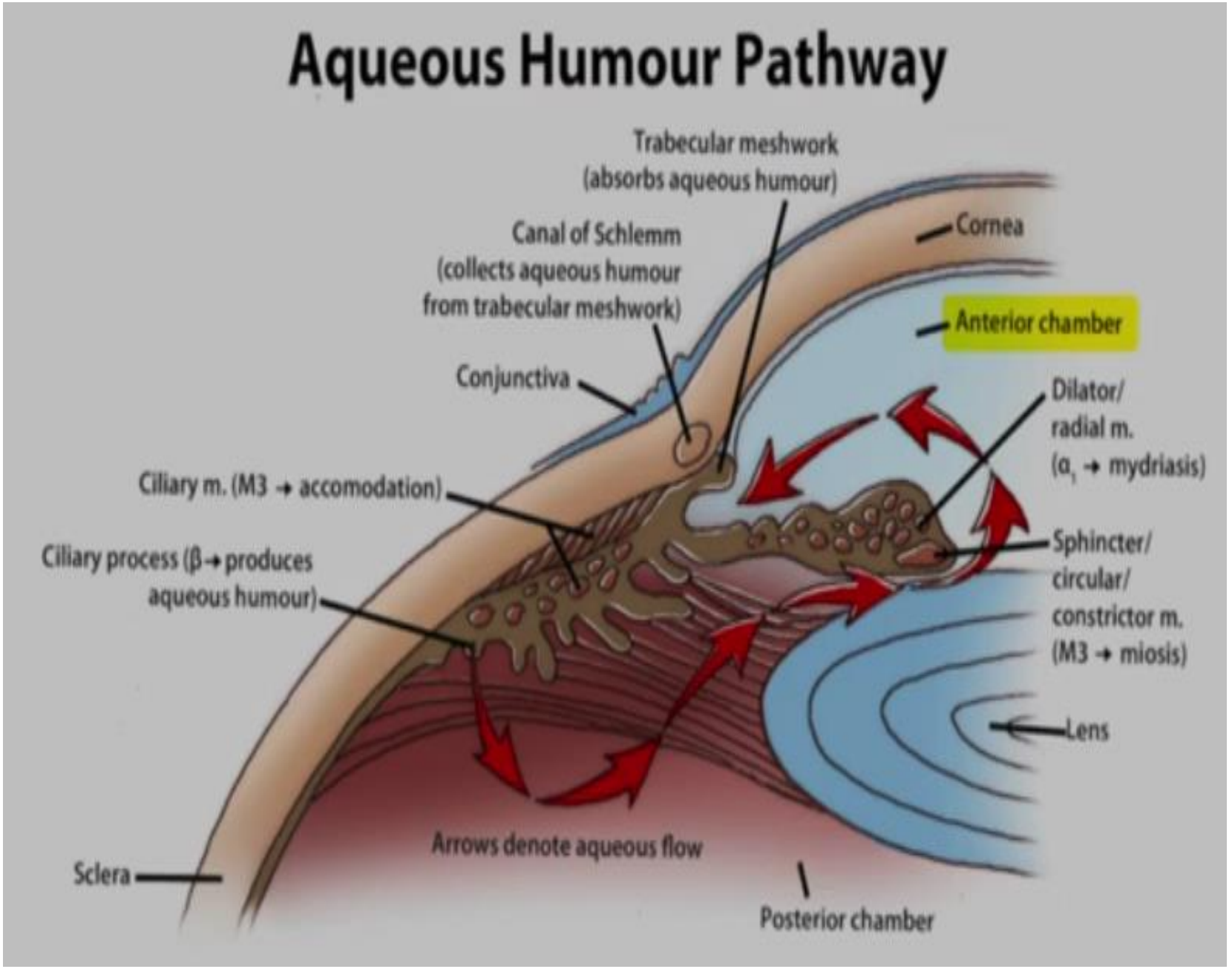
A Closer Look at the Trabecular Meshwork





From www.ahaf.org

Aqueous Humour Pathway



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 Methacholine	Induction of miosis in surgery Open angle glaucoma
Pilocarpine	In open angle glaucoma
Physostigmine Ecothiophate Isoflurophate	Glaucoma, accommodative esotropia

Cholinergic (Muscarininc) antagonists

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

Ocular actions of 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 (myopia, hyperopia).

SYMPATHETIC DRUGS

Adrenergic agonists

Non-selective agonists (α_1, α_2, β_1, β_2)

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

Selective agonists (α1) e.g. phenylephrine

Selective agonists (α2) e.g. apraclonidine

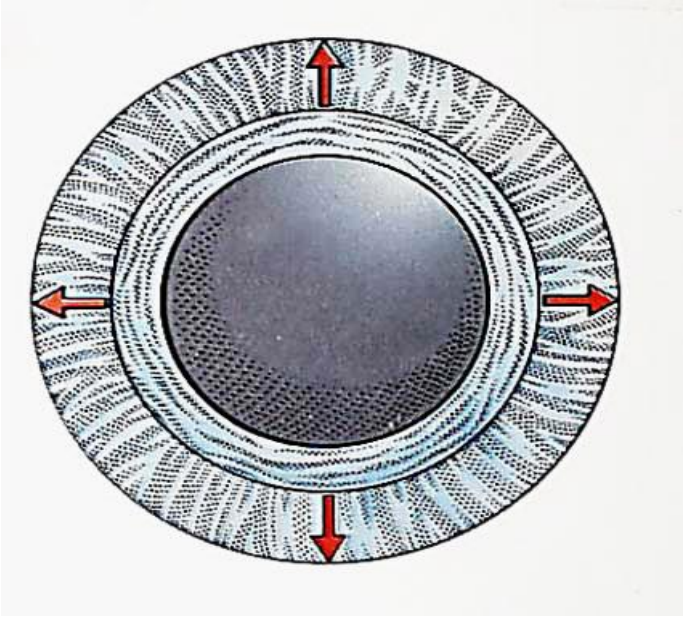
Non Selective β blockers e.g. timolol, carteolol

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 **radial muscle** **circular muscle**	No effect Contraction (miosis) M3	Contraction (Mydriasis) α1 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 (α_1, α_2, β_1, β_2)

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

Mechanism:

↓ aqueous humor production through vasoconstriction of ciliary body blood vessels.

↑ 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:

Bradycardia, hypotension.

β blockers

- **Non-selective:** timolol, carteolol
- **Selective β_1** : betaxolol "cardioselective"
- Given topically as eye drops

Mechanism:

Act on epithelium of 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 :

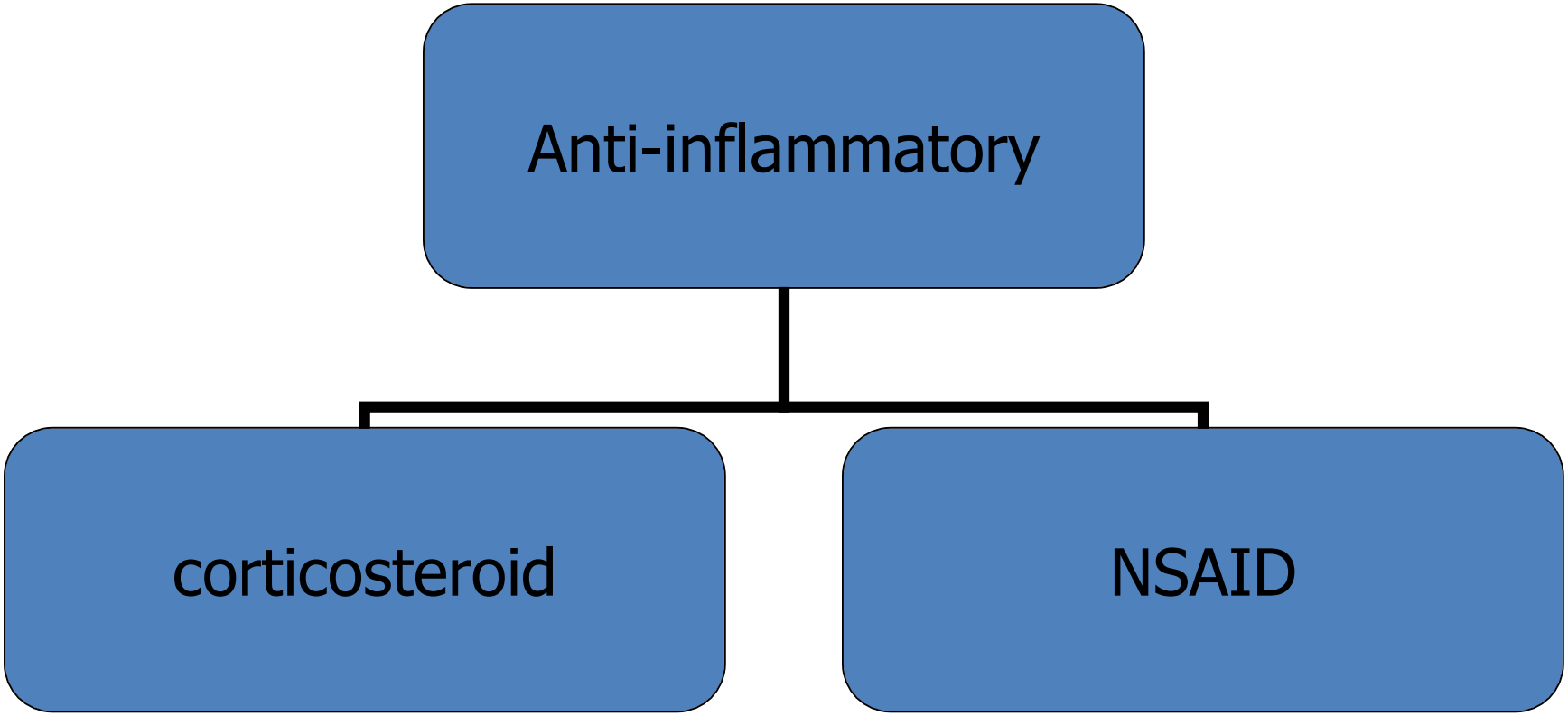
- **Oral Acetazolamide**
- **Topical cholinomimetics** e.g.: pilocarpine
- **Osmotic agents:** hypertonic solutions of (Mannitol, Glycerol).
- **Analgesics:** pethidine or morphine (for pain)

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

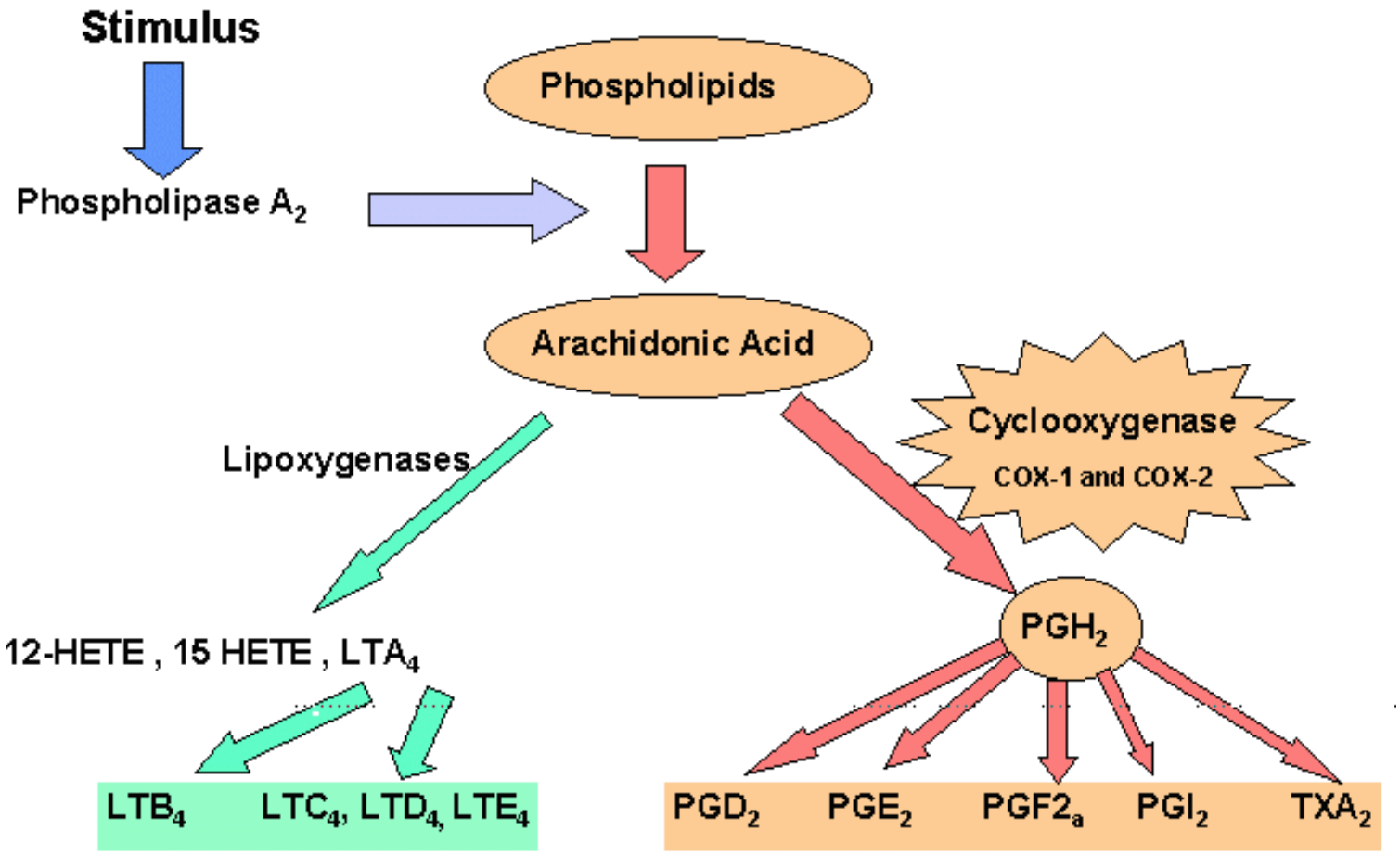
- E.g. prednisolone, dexamethasone, hydrocortisone
- **Uses:** anterior uveitis, severe allergic conjunctivitis, scleritis, prevention and suppression of corneal graft rejection.

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**

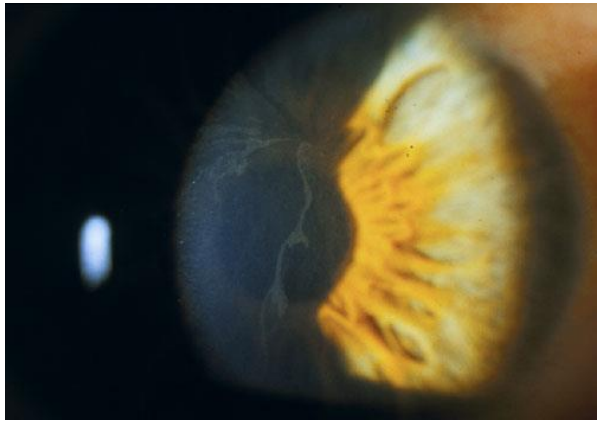
Mechanism: inhibition of cyclo-oxygenase

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