

Pharmacology of The Eye **(Ocular Pharmacology)**

Autonomic Innervation of the Eye:

1. Sympathetic innervation:

- To dilator pupillae muscle = DPM: causes active mydriasis.
- To conjunctival blood vessels: causes V.C. and decongestion.
- These actions are due to stimulation of α_1 -receptors.

2. Parasympathetic innervation

- (through oculomotor nerve = 3rd cranial nerve):
- To constrictor pupillae muscle = CPM: causes miosis.
- To ciliary muscle: causes accommodation to near vision.
- Widening of the spaces of Fontana due to miosis, widening of the canal of Schlemm due to contraction of the ciliary muscle, and increased drainage of aqueous humor and decreased IOP.
- To lacrimal glands: increases lacrimation.
- These actions are due to stimulation of muscarinic receptors (M_3).

Autonomic Receptors in the Eye:

- 1. α_1 -receptor:** stimulation of this receptor leads to:
 - a) Active mydriasis due to contraction of DPM.
 - b) V.C. and decongestion of conjunctival blood vessels.
 - c) ↓ Formation of aqueous hum and IOP.
- 2. α_2 -receptor** in the ciliary body: stimulation leads to c-AMP and aqueous humor synthesis, and IOP.
- 3. β -receptor** in the ciliary body: stimulation leads to c-AMP and aqueous humor synthesis.
- 4. M-receptor:** stimulation of this receptor leads to:
 - a) Miosis due to contraction of CPM.
 - b) Accomodation to near vision due to contraction of the ciliary muscle.
 - c) drainage of aqueous humor and IOP.
 - d) V.D. and congestion of conjunctival blood vessels (M_3 -receptors on blood vessels are non-innervated).
 - e) Lacrimation.
- 5. N_m -receptors** in skeletal muscles of the eye lids, stimulation leads to twitches.

Reflexes:

1. **Light reflex:** is abolished by local application of anti-muscarinic drugs (parasympatholytics) as atropine, hyoscine, and synthetic atropine substitutes, and by systemic administration of ganglion blockers.
2. **Sensory reflex** (corneal and conjunctival reflexes): is abolished by local surface anaesthetics as cocaine (causes active mydriasis) and tetracaine (no mydriasis).

Drugs Acting on the Eye**1) Drugs Affecting the Size of the Pupil:****a) Miotics:****1. Muscarinic Agonists (Parasympathomimetics):**

- **Actions:**
Miosis-Accommodation to near vision- drainage of aqueous humor- IOP- Lacrimation- V.D. of conjunctival blood vessels (congestion).
- **Examples:**
Choline esters: *Carbachol- Bethanechol*.
Cholinomimetic alkaloids: *Pilocarpine*.
Reversible anticholinesterases: *Physostigmine-Neostigmine- Demecarium*.
Irreversible anticholinesterases: *Echothiophate-Isofluorophate=DFP* (long acting- better avoid chronic use as it may cause cataract).

N.B.:

Carbachol and all anticholinesterases cause "twitches" of the eye lids because they stimulate N_m-receptors in the skeletal muscles of the eye lids, whereas Pilocarpine, and Bethanechol do not cause twitches as they do not have nicotinic actions.

- **Therapeutic uses:**
 - a) Treatment of glaucoma.
 - b) To counteract mydriatics.
 - c) To cut recent adhesions between iris and lens in cases of iritis, they are used "alternatively" with mydriatics.

2. Guanethidine:

- **Actions:**
Decreases release of noradrenaline from adrenergic (sympathetic) nerves leading to parasympathetic predominance causing miosis and decrease IOP.
- **Therapeutic uses:**
Treatment of glaucoma.

3. Morphine:

- **Action:** morphine causes miosis when given systemically by stimulation of specific opiate receptors in 3rd nerve nucleus (Edinger-Westphal nucleus), this is sometimes known as "central miosis".

N.B.

- Acute morphine toxicity causes severe miosis known as "**Pin Point Pupil=PPP**".
- Miotic action of morphine is antagonized by: local atropine and systemic naloxone (opiate receptor antagonist).

b) Mydriatics:

1. **Active Mydriatics:** they stimulate α_1 -receptors in DPM, either directly or indirectly (see later).

- **Actions:**

- a) Active mydriasis.
- b) Light reflex is present (intact-preserved), and no cycloplegia.
- c) V.C. and decongestion of conjunctival blood vessels.

- **They include:**

- a) Direct α_1 -Agonists (direct sympathomimetics): *Phenylephrine*.
- b) Indirect (indirect sympathomimetics): *Amphetamine* stimulates noradrenaline release from adrenergic nerves.
- c) Dual action: *Ephedrine* (remember that ephedrine does not cause mydriasis in negroes=racial tolerance).

- **Therapeutic uses:**

- a) Fundus examination.
- b) Decongestion.
- c) Alternatively with miotics to cut recent adhesions in iritis.

N.B.:

1. Adrenaline applied locally in the eye does not cause mydriasis except in cases of supersensitivity (see adrenaline).
2. Active mydriatics do not cause cycloplegia.

Cocaine:

- Indirect α_1 -agonist by inhibition of neuronal reuptake of noradrenaline (uptake I), and MAO inhibition → accumulation of endogenous noradrenaline at α_1 -stimulation.
- Local surface anaesthetic.
- loss of sensory reflex.

2. Passive Mydriatics:**a) Anti-Muscarinic Drugs (Parasympatholytics):****• Actions:**

1. Passive mydriasis by blocking M-receptors in CPM.
2. Light reflex is absent (abolished).
3. Cycloplegia (paralysis of the ciliary muscle) by blocking M-receptors.
4. Xerophthalmia (dryness of the eye due to block of M-receptors in lacrimal glands).
5. ↓ drainage of aqueous humor and elevation of IOP
6. No effect on conjunctival blood vessels.

• Examples:

1. *Atropine* and *hyoscine* (natural belladonna alkaloids).
2. *Homatropine*, *tropicamide*, *eucatropine*, and *cyclopentolate* (synthetic atropine substitutes).

• Therapeutic uses:

1. Fundus examination (except atropine).
2. Atropine is used in iritis, iridocyclitis, and corneal ulcer and measurement of the errors of refraction in children.

• Contraindication:

Glaucoma.

b) Ganglion Blockers:

They cause passive mydriasis when given systemically.

In Experimental Pharmacology Exam:

An unknown drug is applied locally (topically) into a rabbit's eye, it may produce:

1. **Miosis + Twitches of eye lids = Muscarinic AND Nicotinic agonist (*Carbachol*, *Physostigmine*, *Demecarium*, *Ecothiophate*, and *DFP*).**
2. **Miosis – Twitches of eye lids = Muscarinic agonist WITHOUT nicotinic action (*Bethanechol* and *Pilocarpine*).**
3. **Mydriasis + light reflex + sensory reflex = α_1 -agonist (*Phenylephrine*, *Amphetamine*, and *Ephedrine*).**
4. **Mydriasis + light reflex – sensory reflex = Cocaine.**
5. **Mydriasis – light reflex + sensory reflex = Anti-muscarinic drug (*Atropine*, *Hyoscine*, *Homatropine*, *Tropicamide*, and *Cyclopentolate*).**

GLAUCOMA

- Glaucoma is elevation of IOP (normally IOP is between 15-25 mmHg.).
- It is considered as "imbalance between rate of formation of aqueous humor by the ciliary epithelium and the rate of drainage".
- Drainage of aqueous humor occurs by 2 routes: 1-Conventional route through the trabecular network into the canal of Schlemm, it drains about 90%. 2-Uveo-scleral pathway through the ciliary body into the suprachoroidal space, it drains about 10%.

Types and Treatment:

a) Wide (Open) Angle Glaucoma:

- It is due to imbalance between formation and drainage of aqueous humor. It is usually chronic and is treated medically by:
 1. **Muscarinic agonists** (parasympathomimetics) acting as "miotics" which increase drainage of aqueous humor: *carbachol-bethanechol-pilocarpine-physostigmine-neostigmine-demecarium*

N.B.:

1. Ecothiophate and DFP are long acting but are not preferred as they may produce irritation and congestion, and may induce cataract.
2. Physostigmine use is limited due to allergic reactions.
3. Parasympathomimetics applied locally in the eye may lead to systemic adverse effects as bradycardia and bronchospasm.
 2. **Sympathomimetics (α_1 -Agonists)**: they decrease formation of aqueous humor by V.C.: *adrenaline* (causes irritation and pigmentation of conjunctiva)-*dipivefrin* (prodrug converted into adrenaline inside the eye, more lipophilic and less irritant than adrenaline). They also cause active mydriasis.

N.B.: mydriatics should be avoided in narrow angle glaucoma.

3. Sympathetic Depressants:

- **β -Blockers**: block β -receptors in ciliary body \rightarrow c-AMP \rightarrow \downarrow formation of aqueous humor: *timolol-betaxolol-levobunolol-carateolol*. They do not change the size of the pupil.
(Remember that *timolol* can precipitate asthmatic attacks in susceptible patients, HOW?).
- **α_2 -Agonists**: stimulate α_2 -receptors in the ciliary body \rightarrow c-AMP \rightarrow \downarrow formation of aqueous humor: *apraclonidine-brimonidine*. No change in the size of the pupil.
- **Guanethidine**: inhibits noradrenaline release \rightarrow parasympathetic predominance \rightarrow miosis and increased drainage of aqueous humor.

4. Carbonic Anhydrase Inhibitors:

- They decrease formation of aqueous humor.
- They do not change the size of the pupil.
- They may be given topically as *dorzolamide* and *brinzolamide*, or systemically as *acetazolamide* and *dichlorophenamide*.

5. PGF_{2α}-analogues: they increase drainage of aqueous humor through the uveoscleral outflow, they may cause irritation and pigmentation of the iris. Examples: *latanoprost*, *travoprost*, and *bimatoprost*. No change in pupil size occurs.**b) Narrow (Closed) Angle Glaucoma:**

- It is due to occlusion of the angle of filtration by the root of the iris. It may be acute and is usually treated surgically by iridectomy. Drugs are used to lower IOP before surgery and in acute conditions and include:
 1. **Short acting miotics:** *pilocarpine* (drug of choice), *physostigmine*, *carbachol*. Avoid long acting miotics (organophosphorous compounds as *echothiophate*) as they cause congestion and severe miosis.
 2. **Dehydrating agents (osmotic agents):** *mannitol* (I.V.infusion), *magnesium sulphate* (rectal enema) , *isosorbide* (orally) in acute congestive glaucoma.
 3. **Carbonic Anhydrase Inhibitors:** given locally as *dorzolamide* or orally as *acetazolamide*.
 4. **Alpha₂ agonists as Brimonidine.**

N.B.:

1. Avoid mydriatics in closed angle glaucoma. .
2. Recently Beta blockers are used with pilocarpine.

Drugs Contraindicated in Glaucoma:

- 1) **Antimuscarinic drugs:** *atropine*, *hyoscine*, and synthetic substitutes *homatropine*, *tropicamide*, and *cyclopentolate*.
- 2) **Ganglion blockers:** e.g *trimetaphan*.
- 3) **Drugs with atropine-like action:** 1st-generation antihistaminics-some antiarrhythmic drugs as *disopyramide*-Tricyclic antidepressants-Phenothiazine antipsychotics.
- 4) **Glucocorticoids:** such as *cortisol*, may also cause cataract.
- 5) **Vasodilators:** as *nitrates* and *fenoldopam*.
- 6) **Succinylcholine:** depolarizing neuro-muscular blocker.

Miscellaneous Drugs Affecting The Eye**a) Toxic Drugs on the Eye:**

1. Glucocorticoids: may cause glaucoma and cataract. Immunosuppressive action may cause 2^{ry} infection.
2. Digitalis: causes disturbance of green and yellow vision (chromatopsia).
3. Ethambutol: anti-T.B., causes optic neuritis.
4. Chloroquine: anti-malarial and anti-inflammatory, causes retinopathy.
5. Chlorpromazine: phenothiazine antipsychotic, causes corneal and lens deposits.
6. Indomethacin: NSAID, may cause corneal deposits.
7. Methyl alcohol (Methanol): metabolized into formaldehyde which is retinotoxic causing blindness (see general pharmacology).

b) Diagnostic Drugs used in the Eye:

1. Fluorescein dye: used in diagnosis of corneal ulcers.
2. Hydroxyamphetamine:
 - Amphetamine derivative which stimulates release of noradrenaline from sympathetic post-ganglionic adrenergic neurons. In contrast to amphetamine it has weak CNS actions.
 - It is used to differentiate between pre-ganglionic and post-ganglionic injury in "Horner's syndrome" (injury of the sympathetic supply of the face causing ptosis, miosis, and anhydrosis). Hydroxyamphetamine causes mydriasis in pre-ganglionic lesions but cannot induce mydriasis if there is post-ganglionic lesion.

c) Anti-allergic Drugs in the Eye:

1. Antihistaminics (H₁-Blockers): antazoline.
2. Glucocorticoids: cortisol, prednisolone, dexamethasone.
3. Mast-cell Stabilizers: disodium cromoglycate.

d) Anti-inflammatory Drugs in the Eye:

1. NSAIDs: diclofenac.
2. Steroidal Anti-inflammatory drugs=Glucocorticoids.

e) Local Anaesthetics in the Eye:

1. Surface anaesthetics: tetracaine(no mydriasis)and cocaine (causes active mydriasis and V.C.), used in minor procedures as foreign body extraction.
2. Infiltration anaesthetics: lidocaine and procaine, used in eye surgery as cataract.

f) Treatment of Eye Infections:

1. Antibacterial drugs: chloramphenicol, tobramycin, penicillin, tetracycline, sulphonamides, and norfloxacin.
2. Antiviral drugs: acyclovir in treatment of Herpes simplex virus.
3. Antifungal drugs: amphotericin B, and azoles as ketoconazole.
4. Antiseptic drugs: boric acid lotion and zinc sulphate in conjunctivitis.

g) Conjunctival Irritants:

1. Chloroacetophenone=Tear gas: causes lacrimation.
2. Ethyl morphine: causes irritation of conjunctiva leading to V.D. and stimulates healing of corneal ulcers.