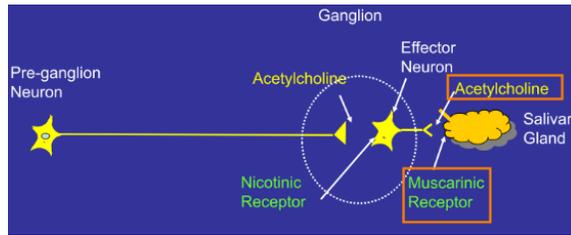


**PNS:**



**Muscarinic receptors:** M<sub>1,3,5</sub> post-synaptic and stimulatory; M<sub>2,4</sub> pre-synaptic & inhibit NT release

M <sub>1</sub>	Salivary gland	Increase saliva
M <sub>2</sub>		
M <sub>3</sub>	Eye	Constriction of pupils
		Contraction of ciliary muscle
		Contraction trabecular meshwork
	Glands	Salivation
	Blood vessels	Dilation (release of NO)
M <sub>4</sub>		
M <sub>5</sub>	CNS	Vascular dilation

**Muscarinic receptors and the eye:**

- Parasympathetic nerves activate M<sub>3</sub> receptors:
  - Globular acinar cells (lacrimal gland) to secrete tears
  - Goblet cells (conjunctival epithelium) to release mucin into tear for lubrication
- Tears spread over eyeball by blinking
- Anticholinergic drugs (muscarinic receptor antagonists) can cause dry eyes by blocking M<sub>3</sub> receptor activation
- Sjorgren’s syndrome pts can have antibodies to the M<sub>3</sub> receptor → dry mouth (xerostomia) & dry eyes (xerophthalmia)

**Pharmacology of iris**

Circular muscle (M <sub>3</sub> )	Contracts → miosis
Radial muscle (α <sub>1</sub> )	Contracts → mydriasis
Sympathetic (M <sub>2</sub> )	Suppresses release (opposes mydriasis)

**Eye drops for pupil dilation**

**Alpha agonists:** increase muscle tone in dilator muscle

- Phenylephrine: dilation w/ minimal cycloplegia in 20-90 minutes, duration 3-8 h

**Muscarinic antagonists:** block contraction of pupillary sphincter muscle & ciliary muscle (cycloplegia at higher concentrations)

- Cyclopentolate: duration of dilation up to 6-24 h
- Tropicamide: duration of dilation up to 4-8 h
- Atropine: duration of dilation for 7-10 days (problematic); antagonist of all subtypes

SEs:

CNS	Drowsy, hallucinations (child/elderly)
CV	Increased HR, faster conduction
RESP	Bronchodilation; decreased secretion
GI	Decreased motility & secretion
GU	Urinary retention
GLANDS	Decreased salivation/sweating (hyperthermia)

**Intraocular pressure:** normal 12 – 15 mmHg

- Aqueous humor fills anterior cavity (nourishes lens, cornea and iris)
- Vitreous humor (clear, gelatinous) fills posterior chamber (99% water w/ collagen & hyaluronan)

**Secretion of aqueous humor:** iris & ciliary body

- Flows from posterior → anterior chamber
- Outflow into venous system
  - Trabecular outflow (80-95%) through trabecular meshwork & Schlemm’s canal
  - Uveoscleral outflow (5-20%) through spaces between bundles of ciliary muscle

Ciliary muscle M <sub>3</sub> contracts	Allows accommodation (moves lens)
	Opens trabecular meshwork
	Increases flow of aqueous humor
Ciliary epithel. β <sub>2</sub> adrenergic	Makes aqueous humor

**Types of glaucoma**

- Open angle: trabecular meshwork open & unobstructed by iris; trabecular/uveoscleral outflow impaired
- Angle-closure: trabecular meshwork obstructed by iris → flow between chambers is blocked
- Secondary: congenital defects, insult or trauma

**Pathogenesis of glaucoma:** optic neuropathy; loss of visual field (peripheral to central field) leading to blindness

- Elevated IOP associated w/ glaucoma, but glaucoma can develop in normal IOP pts
  - Increased IOP damages ganglion cells (mechanical stress) & decreases blood supply to retina (ischemia)
- Loss of blood-retinal barrier with age
- Ischemic injury, mechanical trauma & loss of BRB → inflammation & neurotoxic damage (high glutamate)
- Retinal ganglion cells die → loss of vision

### Specific $\beta$ blockers

- 1) PK properties: many  $\beta$  blockers undergo first-pass metabolism → variability in plasma concentrations = dose requirements can vary greatly amongst individuals
  - Propranolol: non-selective  $\beta$  blocker (hypertension, angina, migraine, essential tremor, decrease sudden death after MI, severe hyperthyroidism)
    - AEs: fatigue, dizziness, depression, nightmares, increases triglyceride levels
- 2) Relative affinities for  $\beta_1$  and  $\beta_2$  receptors
  - Metoprolol ( $\beta_1$  selective): hypertension, angina, after MI, diabetes ( $\beta_2$  receptors in liver needed)
    - AEs: fatigue, dizziness, bradycardia
- 3) Pure antagonists vs. partial agonists (weakly activate  $\beta$  receptors): prevents untoward effects such as precipitation of asthma or excessive bradycardia
  - Acebutolol ( $\beta_1$  antagonist w/ partial  $\beta_1$  agonist properties): hypertension, angina, weak membrane stabilizing activity
    - AEs: fatigue & dizziness (less likely to cause bradycardia or alter plasma lipids)
- 4) Local anesthetic membrane-stabilizing effects: blockade of sodium channels (high concentrations)

### Drugs used for glaucoma

Category	Drug	Mechanism	Local effects	Systemic effects
Muscarinic agonists	Pilocarpine (also for xerostomia)	Increase trabecular outflow	<ul style="list-style-type: none"> <li>• Blurred &amp; dimmed vision</li> <li>• Ciliary muscle spasms → headaches</li> <li>• Cataracts (long-term use)</li> </ul>	
	Carbachol			
	Physostigmine (also for myasthenia gravis)	Indirect-acting cholinergic agonist		
Non-selective $\beta$ blocker	Timolol	<ul style="list-style-type: none"> <li>• Decrease AH production</li> <li>• Increase trabecular outflow</li> </ul>	Dry eye	Bradycardia, fatigue, dizziness, altered TG levels, interference w/ $\beta_2$ asthma drugs
	Levobunolol			
$\beta_1$ selective	Betaxolol	Decrease aqueous humor production (becomes non-selective at high conc.)		Bradycardia, fatigue, dizziness
$\alpha_2$ agonists	Apraclonidine	<ul style="list-style-type: none"> <li>• Decrease AH production</li> <li>• Increase uveoscleral outflow</li> </ul>	<ul style="list-style-type: none"> <li>• Less effective</li> <li>• Allergic conjunctivitis</li> <li>• Sedation</li> </ul>	Hypotension (decreased sympathetic output)
Prostaglandin F2 $\alpha$ analogue	Latanoprost	<ul style="list-style-type: none"> <li>• Relaxes ciliary muscles</li> <li>• Increase matrix metalloproteinase → remove extracellular matrix b/w ciliary muscle cells → increase UV outflow by 60-100%</li> <li>• Increase conventional outflow (widening trabecular spaces and increase flow through Schlemm's canal)</li> </ul>	<ul style="list-style-type: none"> <li>• Conjunctival hyperaemia (red, inflamed eye)</li> <li>• Iris darkening</li> <li>• Increased growth &amp; darkness of eyelashes</li> </ul>	
	Travoprost			
	Bimatoprost			
Carbonic anhydrase inhibitors	Dorzolamide (topical)	Decreases rate of formation of AH by blocking bicarbonate formation	<ul style="list-style-type: none"> <li>• Avoid if known sulfa allergy</li> <li>• Fatigue, depression</li> <li>• Paresthesias</li> <li>• Altered taste</li> </ul>	
	Brinzolamide (topical)			
	Acetazolamide (oral)			