

## DRUGS ON THE EYE

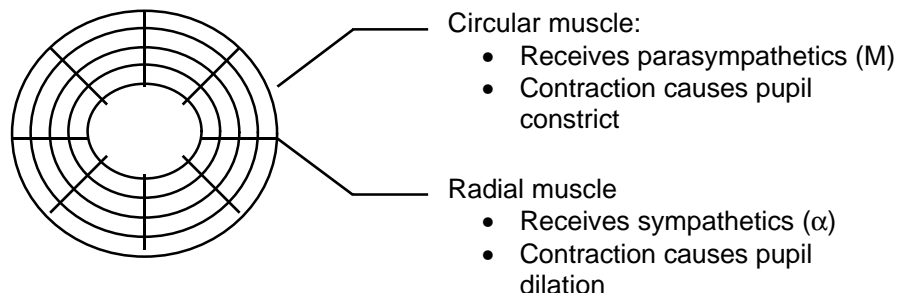
### Pharmacological principles

1. Deliver the agent to the site desired
  2. In the form that is required
  3. In the proper vehicle
  4. At the right concentration
  5. Ensure it only acts where it is intended
- Only in dermatology and ophthalmology can these principles be adhered to properly
  - The eye, like the skin, is an exposed structure, therefore, it is open to the elements and it is possible to apply drugs directly to the surface via drops or ointments.
  - Targets in the eye for the drug to act are:
    - Cornea
    - Iris
    - Conjunctiva
    - Ciliary body
  - In addition, there are various factors which hinder the drug's action, especially if we want the drug to act deep in the eye:
    - The drug needs to be able to penetrate the cornea
    - It needs to be in sufficient concentration as the fluid in the eye (aqueous and vitreous humor) will dilute the drug
    - When applying something to the eye, the natural protective response is to produce tears. This is another factor which tends to dilute the drug.

### Drugs used for ocular procedures

#### MYDRIASIS

- When an ophthalmologist wishes to view the retina, a mydriatic agent is used to dilate the pupil
  - Mydriasis is dilation of the pupil by contracting the radial muscle of the iris



- When an organ receives dual parasympathetic and sympathetic innervation, one tends to dominate
  - In the case of the eye, the parasympathetics dominate under basal conditions (therefore, miosis is the normal)
  - Parasympathetics to the eye controls
    1. Miosis
      - Muscarinic activation of the circular muscle causes pupil constriction (for better day vision)
    2. Accommodation for near vision
      - Muscarinic activation of the ciliary muscle causes contraction which makes the lens thicker, allowing the eye to focus on near objects
    3. Pupillary light reflex

- The most commonly used mydriatics are:
  - A. Muscarinic antagonists
    - **Tropicamide, cyclopentolate (prototype is Atropine)**
    - By blocking the effects of Ach (which are present during basal activity), you stop the constriction, allowing for unopposed sympathetic activation, causing pupil dilation (mydriasis)
    - Side effects:
      - Can't accommodate for near vision (since parasympathetics also control the ciliary muscle which controls the thickness of the lens)
      - Can't stand bright lights (loss of pupillary light reflex)
  - B.  $\alpha$  receptor agonists
    - **Adrenaline, phenylephrine**
    - Often used in conjunction with M antagonists (the mydriatic eye drops contain a combination of  $\alpha$  agonists and M antagonists)
    - The advantage of these is that they do not cause loss of the pupillary light reflex

### LOCAL ANAESTHESIA

- When an ophthalmologist measures the intraocular eye pressure, a machine makes contact with the eye. This can be very uncomfortable, hence the use of local anaesthetic eye drops:
  - **Lignocaine**
  - **Amethocaine**
  - Can also be used for eye surgery.

### Drugs used for the treatment of ocular disorders

#### ANTI INFLAMMATORIES

- Because the eye is exposed, it is subject to drying and inflammation.
  - Inflammation of the eye can be due to:
    1. Presence of a foreign particle
    2. Chemical injury
    3. Allergy
    4. Infection
  - It is important to determine whether the inflammation is due to infection or not, because the treatment differs (giving corticosteroids when there is an infection is a no no!)
- Anti inflammatory preparations contain a mixture of drugs:
  1. Vasoconstrictors
    - The conjunctiva appears very red (bloodshot) due to congestion with blood
    - Vasoconstrictors relieves the congestion
    - $\alpha$  agonists:
      - **Phenylephrine, naphazoline**
  2. Antihistamines
    - Useful for preventing the red eyes as a result of allergy (e.g. hayfever)
    - The histamine released by the mast cells causes vasodilation by binding to H1 receptors on the blood vessels.
    - H1 antagonists:
      - **Antazoline**
  3. NSAIDs
    - Prevent the release of prostaglandins which causes vasodilation and pain
    - **Indomethacin**
  4. Corticosteroids
    - **Prednisolone, betamethasone, medrysone**
    - Can be given systemically
    - Excellent anti inflammatories because they inhibit lots of arms of the inflammatory response:
      - They prevent the release of prostaglandins and leukotrienes
      - Immunosuppressives (do not use if the inflammation is due to infection - you need an intact immune system if it is an infection)

- Target the early and late stages of the immune response
- Prevent cell migration and mediator release
- Corticosteroids also have some severe side effects:
  - A. Glaucoma
  - B. Cataracts

### ANTIMICROBIAL AGENTS

- Inflammation caused by bacteria or viruses require specific treatment to eliminate the organism
- Principles in the treatment:
  1. Accurate diagnosis to identify the cause
  2. Select the best appropriate drug
  3. Minimise the toxic effects (by preventing systemic absorption)
  4. Treat until there is no more staining with fluorescein
    - Fluorescein is used to stain up areas of the cornea which are damaged
- Antibacterial agents:
  - **Chloramphenicol, ciprofloxacin, tetracycline**
  - Need to consider whether a bactericidal or bacteriostatic agent would be useful (normally it would not be an issue, but if the person is immunocompromised, bactericidal agents need to be used)
  - The drugs tend to have an irritant effect - causing lacrimation. This may dilute the drug, therefore need higher concentrations
- Antiviral agents:
  - A common viral infection of the eye is due to herpes
  - Before treatment, wiping debridement is useful
    - Because viruses grow in cells, wiping away infected cells first will lessen the viral load. This prevents the need to give very high concentrations of drugs.
- Antifungal agents:
  - **Amphotericin (drops or ointments)**
  - **IV amphotericin is only used for severe fungal infections**
- Antiseptics:
  - **Aminacrine**

### DRUGS USED IN GLAUCOMA

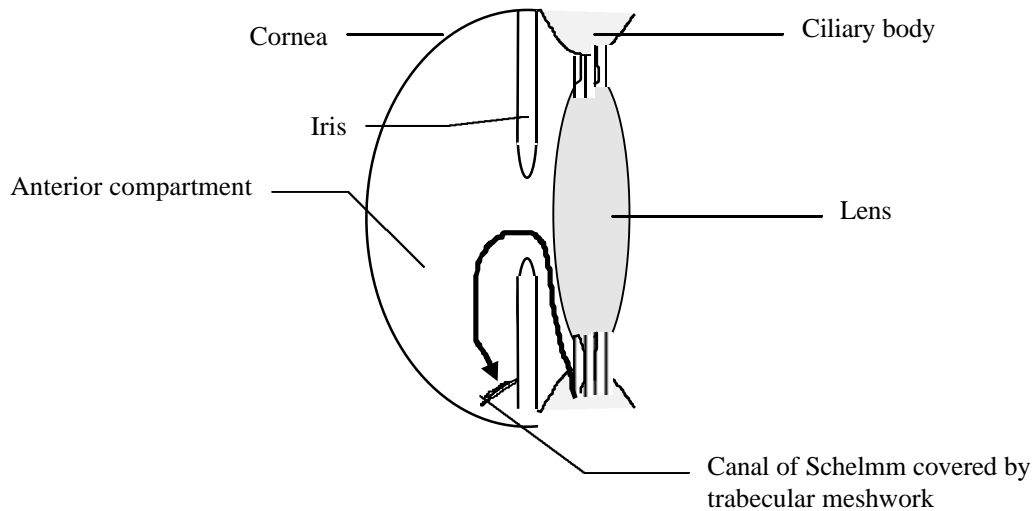
#### Definition

- Glaucoma is a raised intra ocular pressure which can result in visual defects and blindness via compression of the optic disk and nerve
- It is classified as being:
  - Primary:
    - A. Closed angle glaucoma
      - Reduced angle between the cornea and the iris
      - Due to blockage of the trabecular meshwork, preventing drainage of fluid
    - B. Open angle glaucoma
      - Increased angle between the cornea and the iris
      - Due to increased production of fluid by the ciliary body
  - Secondary
    - Drug induced (corticosteroids)
    - Diabetes
    - Congenital

#### Normal aqueous humor circulation

- The aqueous humor is produced by the ciliary body
  - The ciliary body has a very large capillary network
  - The aqueous humor is basically an ultrafiltrate of plasma
  - There are also ions which are actively secreted into the aqueous humor:
    1. The active secretion is dependent on  $\beta$  activation, which causes increases in cAMP
    2. There is also active secretion of  $\text{Na}^+$  via an ATPase

3. There is passive diffusion of  $H_2O$ ,  $Cl^-$  and  $HCO_3^-$ 
  - Formation of  $HCO_3^-$ :
    - $CO_2$  is taken up by the cells in the ciliary body
    - It reacts with water to form  $H_2CO_3$  which then breaks down into  $HCO_3^-$  and  $H^+$  (the process is catalysed by carbonic anhydrase)
  - The aqueous humor flows into the anterior chamber and drains through out of the eye via the canal of Schlemm (which is covered by a trabecular meshwork)



- In closed angle glaucoma, the trabecular meshwork is thickened, so that drainage of the aqueous humor is impaired
- In open angle glaucoma, there is excessive production of aqueous humor

#### Rationale for therapy of glaucoma

- Because glaucoma is due to:
  - A. Impaired outflow, and/or
  - B. Increased production
- In order to treat it, we could:
  - A. Improve outflow
  - B. Inhibit production

#### Improving outflow of aqueous

- Useful for closed angle glaucoma
- To improve outflow, we need to widen the opening to the canal of Schlemm by:
  1. Constricting the circular muscle of the iris, causing pupillary constriction
  2. Contracting the ciliary muscle (causing thickening of the lens)
- Because both these mechanisms are controlled by muscarinic activity, muscarinic agonists will be useful:
  - Muscarinic agonists:
    - **Pilocarpine, carbachol**
    - These agents constrict the pupil (miotics)
    - The problem with these agents is that they are very short acting (due to metabolism by pseudocholinesterases). Therefore, they need to be taken many times a day.
    - In order to overcome this problem, irreversible cholinesterase inhibitors can be used:
      - **Ecothiopate**
    - Side effects:
      - The miosis means that you will have problems with night vision
      - Accommodative spasm (become short sighted)
        - Distance vision is impaired (blurry vision) because the ciliary muscle is contracting - makes lens fatter. Therefore, you can only see near objects clearly. Because most of the day we spend looking at objects in the

distance, it can be very uncomfortable having blurred vision all the time (get headaches)

- Cholinergic drugs also cause vasodilation, and may give some people headaches if the cerebral vessels are vasodilated.
- Cataracts are more likely with ecotiopate
- Contraindications:
  - Young patients
  - Secondary closed angle glaucoma (Why?? I don't know!)

### Reduce aqueous humor formation

#### 1. $\beta$ antagonists

- **Timolol**
- Non selective  $\beta_1$  and  $\beta_2$  antagonist
- Inhibits the cAMP dependent process in the ciliary body
- Adverse effects:
  - Ocular irritation
  - Superficial keratopathy
  - Bronchospasm, heart block, masked hypoglycemia ( $\beta_1$  receptors are required for glycogenolysis and gluconeogenesis)
- Contraindications:
  - Cardiac disease
  - Asthmatics

#### 2. Block the $\text{Na}^+ \text{K}^+$ ATPase

- There are no drugs to do this, and never will be. Why? Because this mechanism is used throughout the body to maintain life - if you block it, you will die!

#### 3. Adrenoceptor agonists

- **Adrenaline**
- Constricts vessels in the ciliary body
- Adverse effects:
  - Allergies
  - Hyperaemia
  - Conjunctival adenochrome deposits
  - Hypertension, palpitations, headache
  - Mydriasis
- Contraindications:
  - Closed angle glaucoma
    - The mydriasis which is produced is due to contraction of the radial muscles in the iris. Contraction of the radial muscles thickens the iris, which can block the opening to the canal of schlemm (see diagram on pg 4)

#### 4. Carbonic anhydrase inhibitors

- **Acetazolamide**
- Can be given intravenously or orally
- Adverse effects:
  - Myopia, Metabolic acidosis, Diuresis, Depression, GI disturbances, blood dyscrasias
- Contraindications:
  - $\text{Na}^+$  and  $\text{K}^+$  deficiency (due to diuretic effect)

#### 5. Hyperosmotic agents

- **Mannitol**
- Given IV for prompt effect in closed angle glaucoma
- It makes the plasma hyperosmotic, so that fluid will tend to stay in the vascular compartment and not diffuse out to become aqueous humor
- Adverse effects:
  - Headache, nausea, vomiting, diuresis, dehydration
- Contraindications:
  - People with oedema or cardiac failure, since the hyperosmotic blood may increase blood volume.