MECHANISMS OF DRUG ACTION ON AQUEOUS HUMOR FORMATION AND DRAINAGE IN POAG

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The Ciliary Body
Ciliary Muscle

- **Longitudinal Bundle**
  - Inserts onto scleral spur and additional tendons extend into and through the meshwork to make attachments directly onto the inner wall of Schlemm’s canal
Cribriform Plexus

Some of the longitudinal bundle attaches to the scleral spur.

Miotics seem to work mainly by holding open Schlemm’s canal, by analogy with the cordae tendinae attached to the mitral and bicuspid valves of the heart.
Parasympathomimetics (cholinergic agents, miotics)

- Most common is Pilocarpine, usually four times per day
- Available as 0.5, 1, 2, 3, 4% gtts and 4% ung
- Side-effects and need for QID dosing have made pilocarpine less popular.
- Carbachol is somewhat stronger.
- Echothiophate (PHOSPHOLINE IODIDE) is essentially unavailable

Parasympathomimetics (cholinergic agents, miotics)

- Periorbital pain, browache, and eye pain
- Blurred vision in older people due pupil restriction forcing all light through densest part of cataract.
- Drug-induced myopia in young patients, who often cannot tolerate these drops.
- Systemic side effects rare with pilocarpine, more common with carbachol, and common with echothiophate.
- Typical parasympathomimetic Sx (e.g. stuffy nose, sweating, increased salivation.
- Rare side effects include retinal detachment. Use with caution above -6D.
- Originally claimed to cause breakdown of the blood-aqueous barrier – recently proven to be incorrect.
Capillaries of the Ciliary Body Stroma
Capillaries of the Ciliary Body Stroma

These capillaries are fenestrated. Using intravascular tracers, that mimic the behavior of plasma proteins, these capillaries are permeable to plasma proteins, accumulating in the ciliary body stroma to a concentration of 75% of that found in the plasma.
Ciliary Process
The Ciliary Epithelium

NPCE cells are joined by tight junctions. Using intravascular tracers, that mimic the behavior of plasma proteins, the intercellular spaces between NPCE cells are seen to be impermeable to these proteins.
Gap Junctions

- Gap junctions allow for electrotonic and metabolic communication between cells.
- Gap junctions join the cells of the layer of the ciliary epithelium to each other and also join the cells of the two layers together.
- The result is that all of the ciliary epithelial cells operate in a coordinated fashion just like a gland.
Gap Junctions in Aqueous Production

Ciliary Body Stroma

- Intercellular communication and coordination via movement of second messengers through lateral gap junctions.
- Ion movement from PCE to NPCE via apical gap junctions.

PCE

NPCE

Posterior chamber
The Diamond-Bossert Model of Standing Gradient Osmotic Flow

- Critical Enzyme Systems
  - Na-K-ATPase
  - Carbonic Anhydrase
Sodium Potassium ATPase

- Activity localized to non-pigmented ciliary epithelium
- Inhibition with ouabain reduces aqueous secretion
Immuno-electron microscopic studies demonstrate the presence of Na-K-ATPase activity in the membranes of the non-pigmented ciliary epithelium.
Inhibition of Na-K-ATPase Reduces Aqueous Flow

- Ouabain added

Na-K-ATPase

Aqueous Flow
Carbonic Anhydrase

\[ \text{H}_2\text{O} + \text{CO}_2 \iff \text{H}_2\text{CO}_3 \iff \text{HCO}_3^- + \text{H}^+ \]

- Catalyzes hydration of carbon dioxide to carbonic acid leading to liberation of hydrogen and bicarbonate atoms

- Enzyme immunohistochemically localized to ciliary epithelia in major processes of pars plicata region only
Carbonic Anhydrase Inhibitors

- NHE-1 and AE2 antiports underlie uptake of Na\(^+\) and Cl\(^-\) in exchange for H\(^+\) and HCO\(_3^\)\(^-\), respectively. Cytoplasmic carbonic anhydrase II enhances the delivery rate of H\(^+\) and HCO\(_3^\)\(^-\). Carbonic anhydrase inhibitors used in the treatment of glaucoma likely reduce inflow and IOP by inhibiting the NHE-1 and AE2 antiports.
Carbonic Anhydrase Inhibitors

- Dorzolamide (TRUSOPT) and brinzolamide (AZOPT) - TID dosing
- Azopt is a suspension – needs shaking

- COSOPT is a combination of dorzolamide (carbonic anhydrase inhibitor) and timolol (beta-blocker) in one bottle.

- The combined effect of these two agents administered together results in additional IOP reduction compared to either component administered alone, but the reduction is not as much when dorzolamide and timolol are administered concomitantly but separately.

Carbonic Anhydrase Inhibitors

If prescribed as part of regular, ongoing therapy, 20% of patients develop a topical allergy. Occasional patients develop side effects similar to those reported for oral agents.

- blurred vision;
- bitter taste in the mouth;
- dry eyes;
- eye irritation or allergy with a red eye or lid margins;
- headache or dizziness; and
- upset stomach.

Remember that these are sulfa-drugs!
Beta-1&2 and Alpha-2 receptors

- Both GTP mediated but in opposite directions.
Beta-Blockers

- Nonselective beta-blockers, timolol (TIMOPTIC, BETIMOL), levobunolol (BETAGAN), carteolol (OCUPRESS), and metipranolol (OPTIPRANOLOL) – better IOP lowering than Beta-1 selective.
- Betoptic is beta-blocker of choice in patients with pulmonary disease, such as asthma or emphysema, and may have less of an effect on blood pressure.
- TIMOLOL: Ophthalmic solution: 0.25%, 0.5%. Usually start with 0.25% BID
- Gel-forming solution (Timoptic-XE) in a 0.25% and 0.5% concentration and must be shaken before use. (corneal infiltrates)

Beta-Blockers

- **Short-term Escape:** Initial response almost always greater than what ultimate response will be after a month – Beta blockade likely results in additional beta receptors being produced early-on to maintain beta stimulation levels at their set point. With more receptors to block, IOP goes even lower, but this receptor number gradually returns to normal and magnitude of effect drops proportionally. Wait a month to determine efficacy in reaching target pressure unless even early results fail to reach target.

- **Long Term Drift:** After the initial plateau is reached, responsiveness may decline between 3-12 months but you have to know to watch for this. Initially, timolol can reduce IOP by 40% but by a year, for many patients the effect is down to 25%.
Beta Blockers

- Ocular side-effects minimal
- Central nervous system side effects include dizziness, depression, fatigue, weakness, decreased exercise tolerance, hallucinations, insomnia, and impotence.
- Hair loss has rarely been reported.
- **CONTRAINDICATIONS**
  TIMOPTIC is contraindicated in patients with
  (1) bronchial asthma or a prior history of it;
  (2) severe chronic obstructive pulmonary disease
  (3) sinus bradycardia;
  (4) second or third degree atrioventricular block;
  (5) overt cardiac failure
  (6) cardiogenic shock; or
  (7) hypersensitivity to any component of this product.
Alpha agonists

- Apraclonidine (IOPIDINE)
  - Apraclonidine has mixed alpha-1 and alpha-2 stimulatory activity.
  - Indicated for short-term adjunctive therapy in patients on maximally tolerated medical therapy who require additional IOP reduction.

- Brimonidine-P (ALPHAGAN-P)
  - Brimonidine has a significantly higher relative selectivity for the alpha-2 receptors
  - 0.2% BID, 0.15% TID, and now 0.1%
  - Claim dual mechanisms of action – decreased secretion and increased uveoscleral outflow*
Alpha agonists

- Most common side effects are ocular burning, itching, brow ache,
- There are reports of lid elevation, dry mucosae (i.e. eye, mouth, and nose)
- Photophobia, headache, dizziness, mild sedation, fatigue and depression.

- Ocular allergy common with IOPIDINE
- ALPHAGAN, was replaced by ALPHAGAN-P, contains purite as a preservative and is less allergenic.

- Precautions: Exercise caution in treating patients with severe cardiovascular disease. And in patients with depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.
Naming the Layers

TM actually extends from Schwalbe’s line to iris root.

Gonioscopic nomenclature confusing because two “layers” are named for what we see through the transparent meshwork and one of them, the layer called the trabecular meshwork is not.
The outflow pathways lie tucked under the scleral rim, requiring us to bend light around a corner to see the entrance clinically.
Pigment Distribution in Normal Angle
The JCT Region
Aqueous outflow is non-uniform. When the JCT region and inner wall are in normal proximity, there are preferential pathways for reaching the inner wall at any given time. This tends to funnel flow to certain parts, creating a back pressure that is resistance to outflow. If we loosen the cytoskeleton of JCT and inner wall cells, the JCT expands, the flow is dispersed, the funneling effect disappears and outflow facility increase (i.e. IOP goes down).
Rho-kinase inhibitors such as Y-27632 (Y-27) affect actomyosin cytoskeletal networks and has been shown to significantly increase outflow facility (C) in enucleated porcine and rabbit eyes, as well as in vivo monkey eyes without obvious toxicity. They alter cytoskeleton in a way that seems to “loosen the meshwork”, thereby increasing outflow.

Effect of Rho-kinase inhibitors on the Outflow Pathways
In December, 2017, Aerie Pharmaceuticals Inc announced that the U.S. Food and Drug Administration approved its eyedrop, Rhopressa, as a treatment for glaucoma, two months ahead of the expected date.

Roclatan combines Rhopressa with a prostanoid.
Vyzulta – Valeant in Canada (which owned B&L)

- Vyzulta combines a prostanoid with a molecule that becomes a nitric oxide donor and has been shown to augment BOTH outflow pathways.

- Latanoprostene bunod is a butylated (i.e. 4 carbon chain) molecule, attached to a nitric oxide donor – hence bunod

- Nitric oxide has been shown to also relax the TM and the ciliary muscle, thus facilitating trabecular outflow
Giant Vacuoles & Pores
Within the wall of the giant vacuole you will find an opening into the vacuole from the JCT region and a much smaller opening in the lumen of Schlemm’s canal.

These occur ONLY under conditions of active aqueous flow.
Collector Channels
Outflow Beyond Schlemm’s Canal

The role of episcleral venous pressure
Goldmann Equation

\[ \Delta P = P_i - P_e \quad \text{and} \quad F = C_{tm} (P_i - P_e) \]

Where:

\( P_i \) = Intraocular pressure in mm Hg

\( P_e \) = Episcleral venous pressure in mm Hg

\( C_{tm} \) = Facility of trabecular outflow

\( F \) = Aqueous Outflow in microliters/min

At Steady State \( F - F_{in} = F_{out} \)
Goldmann Equation

\[ F_{in} = F_{out} = Ctm \ (P_i - P_e) + F_u \]

Assuming:

\[ F_{in} = F_{out} = 2.5 \text{ microliters/min} \]

\[ Ctm = 0.3 \text{ microliters/min/mm Hg} \]

\[ P_i = 16 \text{ mm Hg} \]

\[ P_e = 9 \text{ mm Hg} \]

\[ F_u = 0.4 \text{ microliters/min} \]
Uveoscleral Outflow Pathway
Prostaglandins are arachidonic acid metabolites that are elevated by inflammation, including in anterior uveitis.

These endogenously produced prostaglandins increase uveoscleral outflow much in the same way that Xalatan does.

\[ \Delta P = P_i - P_e \quad \text{and} \quad F = C_{tm} (P_i - P_e) + F_u \]
The Role of Prostanoids on Fuveoscleral

- Prostanoids lead to breakdown of connective tissue matrix between smooth muscle fascicles of ciliary muscle
- MMPs / TIMPs
- There is newer evidence that PG’s also assist trabecular outflow but the mechanism remains uncertain
Prostaglandin Analogues (Prostanoids)

- First was Latanoprost (XALATAN)
- Travoprost (TRAVATAN)
- Bimatoprost (LUMIGAN)
- Unoprostone (RESCULA) – approved as second line drug – only for those who fail to respond to others

- Most common first line drugs. Excellent safety profile and once a day dosing, h.s.
- Can be combined with beta-blocker if required.

Prostaglandin Analogues

- Conjunctival redness is common (with itching if allergic)
  - More common with travoprost and bimatoprost than with latanoprost.
- Darkening of iris may occur. Brown eyes and pure blue eyes are not affected. Intermediate colors most affected. Beginning around pupil and spreading peripherally.
- Increased length, thickness and darkness of lashes
- Reversible darkening of the eyelid skin darkening may also occur.

Flareups of uveitis and CME may occur, especially in those who are post-cataract surgery.

- Some systemic side effects are now beginning to be reported.
  - Gastrointestinal disturbances similar ASA or NSAIDS may occur
  - Rarely, chest pains or palpitations
Additional Reading