Introduction
The primary goal of glaucoma therapy is to stop the loss of retinal ganglion cells, by rescuing injured cells or regenerating new, functional cells, to replace those that are lost. The classical antiglaucoma drugs are used to reduce intraocular pressure (IOP), arguably the most important risk factor for glaucomatous optic neuropathy. Although reducing IOP is often efficacious, in many cases achieving an appropriate target IOP for an individual patient, may not halt progression. In the late 1970’s “neuroprotection” was introduced as a concept whose principle function is to protect retinal ganglion cells (RGC), utilizing approaches in addition to modulating IOP.

CLASSIFICATION OF OCULAR HYPOTENSIVE AGENTS
1) Natural products: Cannabinoids
2) Activators of extracellular matrix hydrolysis: Matrix metalloproteinases (MMPs)
3) Cytoskeleton modulator: Ethacrynic acid
4) Protein kinase inhibitors:
5) Compounds that increase cyclic GMP
6) Neuroprotectors

1. CANNABINOIDS:
   Mechanism of action:
   a) Vasodilation of efferent vessels of anterior uvea.
   b) Modification of surface membrane glycoprotein residues in the ciliary epithelium.
   c) Increased facility of outflow.

   The pharmacology of the cannabinoids includes the cannabinoid (CB) receptors Type 1 and Type 2 or CB1 and CB2, respectively, transporters and enzymes that break down these molecules. The CB1 receptors are present in the ciliary body of humans and rats.

   Side effects: Tachycardia, euphoria, hypotension, conjunctival hyperemia, pulmonary fibrosis and impaired neurological behavior. In particular, the most disturbing side effect is hypotension which may be associated with reduced perfusion of the optic nerve head and could be detrimental in protecting against progressive atrophic optic neuropathy. These side effects of cannabinoids seriously limit their use in the treatment of glaucoma.

2) Activators of extracellular matrix hydrolysis group:
   Mechanism of action: An excessive accumulation of extracellular matrix material in the trabecular meshwork (TM) of glaucomatous eyes likely contributes to decreased aqueous outflow. Therefore therapeutic manipulations that eliminate the excessive ECM should theoretically improve outflow facility and consequently lower IOP.

   Current drug under study from this group:
   a) MMPs: Activation of these enzymes reduces the excessive accumulation of ECM molecules, such as proteoglycans, collagens, fibronectins and laminin in the glaucomatous eye and in turn decreases hydrodynamic resistance of the outflow pathway.

   Disadvantages: MMPs being proteins of large molecular mass are not practical as medical treatment.

   b) Inducers of MMPs: Tert-butyhydroquinone can upregulate MMP3 expression in the TM cells and increase aqueous outflow facility in glaucoma.

   c) Activators of glycosaminoglycan degradation products: Products that catalyse the hydrolysis of GAGs stimulate the degradation of ECM in the TM. GAG degrading enzymes, hyaluronidase and chondroitinase decrease IOP in study models consistently. Similar to MMPs, these enzymes are also not practical for clinical use, as they are larger molecules.

3) Cellular cytoskeleton modulators
Ethacrynic acid is the prototypic agent in this group. It is a sulfhydryl reactive diuretic that disrupts the cytoskeleton...
(microfilaments, microtubules, intermediate filaments), which is thought to alter TM shape and these changes may be sufficient to alter the local geometry of the outflow pathway, and consequently increase aqueous outflow.

**Drugs under study from this group:**

a) Ethacrynic acid  
b) Latrunculin B  
c) Swinholide A

**Disadvantages:** Poor corneal penetration, corneal toxicity and TM toxicity mainly for ethacrynic acid. Latrunculins do not adversely affect the cornea and hence is now in clinical trials.

4) **Protein kinase inhibitors:**

**Mechanism of action:** Exact mechanism is not fully understood. They likely increase the aqueous outflow by affecting cytoskeleton of TM or Schlemm’s canal endothelial cells.

**Drugs under study**

a) Rho kinase Inhibitors  
b) Broad spectrum kinase inhibitors H-7  
c) Inhibitors of protein kinase c

Rho-kinase inhibitors: There are 2 kinds of Rho kinases, ROCK1 and ROCK2, which are serine-threonine kinases that are downstream effectors of Rho GTPase. They regulate smooth muscle contraction in a calcium independent manner. By targeting ROCK activity in the aqueous humour outflow pathway with selective inhibitors, outflow facility through TM is increased leading to decreased IOP. Several ROCK inhibitors (INS117548, DE-104, RK1983) are in clinical trials.

5) **Compounds that increase cGMP:**

**Mechanism of action:** cGMP affects both aqueous production and outflow. Activation of GMP dependent protein kinases, which by phosphorylation, leads to functional changes of various proteins. e.g. an inhibition of Na-K ATPase, leads to decrease in aqueous production.

**Drugs under study from this group:**

a) Nitric oxide (NO) donors: Nitroglycerine, Isosorbide dinitrate, Sodium nitrite, Hydralazine, Minoxidil, Sodium nitroprusside.  
b) Natriuretic peptides: Atrial natriuretic peptide (ANP), Brain derived natriuretic peptide (BNP), C-type natriuretic peptide.  
c) cGMP analogues: Cell permeable analogues of cGMP.

Intracellular cGMP can also be increased by activation of guanylyl cyclases. Nitric oxide (NO) and compounds that release NO (NO donors) are activators of soluble guanylyl cyclases. Both NO donors and natriuretic peptides are effective IOP lowering compounds.

6) **Neuroprotectors:**

**Rationale for use of neuroprotectors:** It has been hypothesized that intravitreal or intraretinal glutamate levels that are neurotoxic to ganglion cells play a role in glaucoma and hence drugs which work against these agents can help in glaucoma management. They are also supposed to enhance the vascular supply and decrease proapoptotic factors.

**Drugs under study from this group:**

a) Glutamate receptor antagonist: NMDA receptor antagonist-Memantine.  
b) Calcium channel blocker-Nimodipine²  
c) Alpha agonists-Brimonidine  
d) Neurotrophic factors-Neurotrophin 3  
e) Apoptotic inhibitors: Cytochrome c release inhibitors, caspase inhibitors

**a) Memantine**

- **N-Methyl D Aspartate (NMDA) receptor antagonist:**  
  **Mechanism of action:** The NMDA receptor is an ion channel that is activated by glutamate, allowing extracellular calcium to enter the cell. In normal physiological conditions, the NMDA receptor has an important role in neurophysiological process such as memory. However, excessive activation of the NMDA signaling cascade leads to “excitotoxicity” wherein intracellular calcium overload neurons and causes cell death through apoptosis. Memantine blocks the excessive glutamate stimulation of NMDA receptor of the regional ganglion cells and protects it from calcium mediated apoptosis.

**Uses:** To treat CNS disorders like Parkinson disease, Alzheimer’s disease. Currently being studied as a neuroprotective agent in glaucoma.

**b) Calcium channel blockers:**  
Nimodipine produces vasodilation by inhibiting entry of calcium into vascular smooth muscle cells. Hence may protect the optic nerve head by improving vascular perfusion. But, the systemic side effects of CCBs do not support the use of this class of drugs for the routine management of glaucoma.
c) Neurotrophic factors: Neurotrophins are peptides that have an important role in development and maintenance of various neuronal population. Protein derived neurotrophic factor neurotrophin 3 and nerve growth factor have differential effects in the cell survival promotion, differentiation or demise. The role of these biologically active peptides and their receptors in relation to survival and death of ganglion cells is under study.

d) Apoptosis Inhibitors: Caspases are family of proteases that executing the dismantling and demolition of cells undergoing apoptosis. Caspases 8 and 9 have been shown to be activated in experimental glaucoma. Suppression of apoptosis using caspases inhibitors is an approach that has been explored with modest success.

e) Nitric oxide synthase Inhibitors:
Aminoguanidine: NO is a gaseous second messenger molecule. It has both physiological and pathologic function in blood flow, immune response and neuronal communication. The expression of NO is regulated by 3 different forms of NO synthase (NOS): Endothelial NOS (eNOS), Neuronal NOS (nNOS), inducible NOS (iNOS).

Role of NO in eye: Excessive NO generated by iNOS in optic nerve astrocytes and microglia are associated with optic nerve damage. Aminoguanidine, by inhibiting iNOS was shown to prevent retinal ganglion cell loss.

IMMUNOMODULATION
It has been proposed that immune system plays a key role in the ability of optic nerve and retina to withstand glaucoma. The mechanism involves recruitment of both innate and adaptive immune cells that together create a protective niche to halt progression of glaucoma eg: therapeutic vaccination with glatiramer acetate (cop1).

Other newer agents:
1) Tetrahydro cortisol: A metabolite of cortisol shown to lower the dexamethasone induced ocular hypertension.

2) Mifepristone: A specific glucocorticoid receptor antagonist lowers IOP.

3) Spiranolactone: A synthetic steroid aldosterone antagonist with potassium sparing diuretic action, produces significant lowering of IOP in glaucoma patients.

4) Antazoline: An antihistamine, shown to lower the IOP following topical administration apparently by decreasing aqueous production.

5) Melatonin: A pineal hormone that reduces IOP. Demeclocycline, a tetracycline derivative also lowers IOP by reducing aqueous production.

6) Ginkgobiloba extract: Leaf extracts of the ginkgo tree have many neuroprotective properties applicable to the treatment of non IOP dependent risk factors for glaucomatous damage. It exerts significant protective effects against free radical damage and lipid peroxidation. It can scavenge NO and also reduce glutamate induced elevation of calcium concentration and inhibits apoptosis. It also preserves mitochondrial metabolism.

References: