

# Drug Targets and its Delivery in Glaucoma -Current Trend and Future Prospects

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## Editorial

### Therapeutic Role of Drugs and Methods of Drug Delivery

Topical route of drug delivery always remained a route of choice for delivering all glaucoma [1] medications rather than systemic route. Upon topical instillation drug reaches interior tissues of eye mainly through corneal route and route and therefore epithelial and stromal layer of the cornea act as barrier to transcorneal permeability of both hydrophilic and lipophilic drugs respectively. Transcellular and Para cellular pathways are the two major corneal transportation routes for the topically applied drugs. Lipophilic drugs cross the cornea through transcellular pathway while the hydrophilic drugs cross through para cellular pathway. For treatment of glaucoma effective drugs are present mainly beta blockers, cholinergic agonists, carbonic anhydrase inhibitors, adrenergic agonists and prostaglandin derivatives but lack effective delivery system to improve patient care and clinical outcomes. Currently available drugs for ocular conditions need to be administered two or more i.e. multiple times a day, as well the poor patient adherence makes the treatment less clinically effective. Studies suggest that <1% of topically administered drug reaches aqueous humor. Up to 80% of systemic absorption of drug occurs followed by topical administration of eye drop causing systemic side effects.

Thus all these factors make topical ocular drug delivery challenging prominently in infants and elderly due to poor adherence and systemic side effects. Novel drug delivery systems such as micro emulsions [2,3], liposomes, dendrimers, nanoparticles, and transparent high viscosity gels have a improved corneal permeation and proven to have a great potential to overcome the problems of patient compliance and provide local, sustained delivery of drugs along with minimizing side effects. Furthermore it is known that  $\beta$ -blockers and adrenergic agents reduce choroidal and optic disc blood flow. Timolol has a better influence on visual field and is considered as an outstanding agent for the management of glaucoma. Latanoprost and brimonidine represent a promising

approach to Intra ocular pressure (IOP) lowering with the potential of enhancing retinal ganglion cell survival. In addition, retinal ganglionic cell (RGC) death elicited by the high levels of glutamate may be overcome by neuroprotective action. These novel targets are ongoing areas of research interests for future glaucoma management.

### Neuroprotection

Neuroprotection approach [4,5] involves direct protection of optic nerves (marginally damaged, undamaged but at risk) through the promotion of cellular survival or inhibition of cell death signals. Recent research in the field of neuroprotection in glaucoma has triggered focusing on to various receptor systems.

### N-Methyl-D-Aspartate (NMDA) and $\alpha$ -2 Adrenergic Receptor Systems

This receptor can be probed among one of the promising future treatment targets. Brimonidine (BMD), a specific  $\alpha$ -2 adrenoceptor agonist, and is found to protect against loss in mitochondrial membrane potential during oxidative stress, and preserve anterograde axonal transport. Secondly Memantine, which is a selective blocker of the NMDA-type glutamatergic type ion channel. It has unique open channel blocker properties that result in a preferential inhibition of excessive (excitotoxic) neuronal activation by high levels of glutamate without interfering with the channel's normal functions. Research in animal glaucoma model evidenced with neuroprotective effects with remarkable shrinking observed in the lateral geniculate nucleus. Both drugs are currently in clinical trials for glaucoma.

Apart from the above two targets several other targets have been proposed for neuroprotection. Adenylate cyclase receptor system activation. Forskolin is a diterpene isolated from the root extract of *Coleus forskohlii* species which activates adenylate cyclase (ACL). ACL activation produces outflow of aqueous humor in ciliary body and trabecular meshwork thereby regulates

increased IOP. Evidences are found in Saffron (*Crocus sativus*) which is a traditional antioxidant agent with key ingredient crocin and crocetin, reduced elevated IOP in glaucoma patients. It also appeared to reverse the effects of photo oxidative toxicity induced in experimental rat models. Citicholine an intermediate in the synthesis of phospholipids such as phosphatidyl choline is found to show neuromodulator and a protective role in RGC's. Citicoline has been shown to protect the retina in vivo against kainate-induced neurotoxicity.

Melatonin a hormone secreted during dark hours by pineal gland. It modulates the body's sleep pattern. Melatonin receptors are found in all the cells of body also in the eye, mainly in the retina and ciliary body. It protects human retinal pigment epithelial cells against oxidative stress and slows down photoreceptor degeneration. Presence of melatonin receptors in ciliary body also suggests that they are involved in IOP regulation by regulating release of cyclic AMP. Due to presence of large number of melatonin receptors in eye, it has becoming attention-grabbing for development of new targets. Few of the naturally occurring plant extracts have shown neuroprotective effects in conditions of increased IOP such as Ginkgo biloba Extract, Epigallocatechin Gallate, Resveratrol, and Rutin. These compounds are currently under extensive investigation and under clinical studies.



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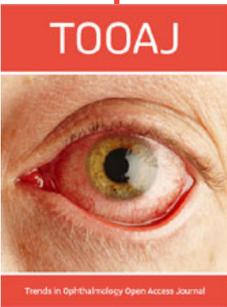
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## Conclusion

Among recent decades ample of research in ocular drug delivery technologies evolved with constant progress in newer delivery methods and devices, nevertheless not a single one could emerge as effectual as eye drops. Still trials are ongoing in the search of effective ocular drug delivery. Even though IOP reduction remains main stay for glaucoma management, there is always scope in investigating new targets that could mitigate the progression of apoptosis and degeneration of optic nerve and provide neuroprotection to RGC's.

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