# Serotonin modulators are neuroprotective in the eye. Hype or Hope?

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## INTRODUCTION

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- 285 million people are estimated to be visually impaired worldwide.
- Diabetic retinopathy is responsible for 4.8% of the cases of blindness worldwide.
- It is estimated that 66.8 million people have glaucoma worldwide.
- Around 30% of people who are over 75 have early signs of AMD.
- The annual cost of adult vision problems in the U.S. comes to approximately $51.4 billion. Blindness and vision impairment cost the Irish State €205 million in 2010, yet up to €76 million could potentially be saved.
- The global ophthalmic devices market is projected to be worth $48.7 billion in 2020, up from $29.1 billion in this year [2014].

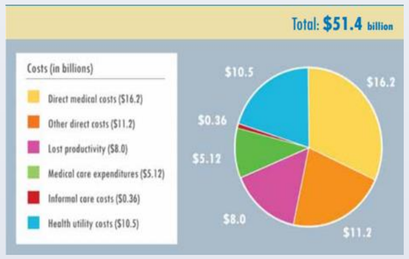


Figure 1. Total Annual Economic Impact of Vision Problems in the U.S.

### ABSTRACT

Neurodegeneration is a principle cause of blindness associated with diseases such as Glaucoma, Age Related Macular Degeneration and Diabetic Retinopathy. Here we critically reviewed the potential use of serotonin modulators in the treatment of neuronal degeneration in the eye.

### SEROTONIN

- A monoamine neurotransmitter
- Primarily found in the GIT, Platelets and the CNS.
- It is biochemically derived from tryptophan.
- Plays a role in controlling mood, social behaviour, cognition, appetite and digestion.
- Interacts with the 5HT1A and the 5HT7 Receptors in the Eye.
- The 5HT1A is negatively coupled to cAMP via Gi proteins, while the 5HT7 increases cAMP levels via Gs proteins.
- There are several mechanisms, one of which is the inactivation of Capase 3 and activation of the MAPK signalling pathway increasing the expression of anti-apoptotic proteins. [1]

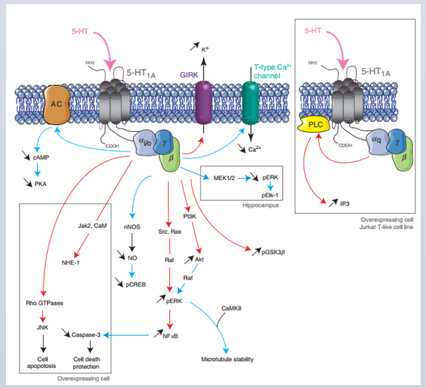


Figure 2. 5-HT1A receptor signaling pathways

## DISEASES

### GLAUCOMA

- Leading Cause of Irreversible Blindness
- Associated with degeneration of the Retinal Ganglion Cells (RGCs), the trabecular network and the optic nerve.
- Characterized by Elevated Intraocular Pressure (IOP) and Optic Disc Cupping.
- Elevated IOP is a contributing factor to the degeneration of the delicate fibres which make up the optic nerve.
- Blind Spots develop as more of the nerve fibres are damaged.
- Damage to the optic nerve head, the trabecular meshwork and the RGCs is responsible for vision loss experienced by patients who suffer from this condition.
- Once damage occurs to the optic nerve, vision loss in permanent.
- There are two major types of Glaucoma: Primary Open Angle
  Acute Angle Closure

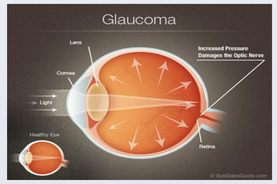


Figure 3. Glaucoma

### AGE-RELATED MACULAR DEGENERATION

- Loss of vision in the centre of the visual field, the macula, because of damage to the tissue complex
- Dry Form- extracellular debris called drusen accumulating between the retina and the choroid - atrophy and scarring to the retina.
- Wet (exudative) form - blood vessels grow up (VEGF) from the choroid behind the retina - leak an exudate and fluid and cause haemorrhaging.
- Risk - Variants in genes that code for components of the alternative pathway of the complement cascade at the RCA (regulator of complement activator) locus on chromosome 1
- Advanced glycation end products (AGE) deposits may induce receptor-mediated activation of RPE/photoreceptor cells, leading to disease progression in the aging human retinas

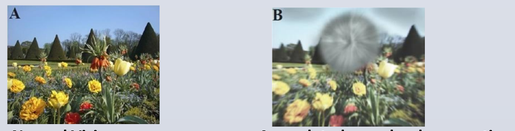


Figure 4. Normal vs. Age Related Macular Degeneration

### DIABETIC RETINOPATHY

- Secondary microvascular complication of diabetes mellitus
- Caused when the small blood vessels in the retinal lining become leaky or blocked and lead to damaged sight.
- Categories of DR are:
  - -Background retinopathy
  - -Moderate Non-proliferative diabetic retinopathy
  - -Severe Non-proliferative diabetic retinopathy
  - -Proliferative
  - -Diabetic macular oedema

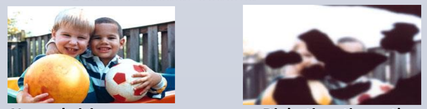


Figure 5. Normal versus affected vision

## CURRENT TREATMENTS

| u | Target | Method of Action | Advantages | Disadvantages |
|---|---|---|---|---|
| **Glaucoma: Pilocarpine** | Muscarinic Receptor | -Binds to the muscarinic receptor. - this causes contraction of the cillary body, increasing drainage through the trabecular meshwork -it also causes pupil constriction, to remove the folds, increasing drainage further. | - eye drop form (easy to use and non-invasive) | - eye drop form (low absorption and short contact time) -administered up to 6 times a day -drug interaction with anticholinergics -impaired vision due to spherical lens shape - parasympathetic side effects -paradoxical hypertension |
| **Glaucoma: Timolol** | β-adrenergic receptor | -binds to β2 receptor, blocking its action -this blocks activation of adenylyl cyclase -this results in decreased aqueous humour formation and secretion | -administered 1 or 2 times daily (less than pilocarpine) - eye drop form | -administered 1 or 2 times a day (inconvienient) -eye drop form -systemic side effects such as bronchospasm and brachycardia |
| **AMD: Lutein** | Reactive oxygen species | - react with active oxygen species, producing biologically active degradation products. -provides protection against phototoxic damage by filtering out blue and near UV light. | -taken orally as a supplement (convienent) -very little side effects | -taken orally (needs to reach sufficicent concentration in the eye, hard to cross blood-retinal barrier) |
| **AMD: Lucentis** | Vascular endothelial growth factor receptor | -binds to and inhibits the activity of VEGF at its receptor -this reduces the growth of abnormal blood vessels in the retina | -injection into the eye (penetrates cornea) -reaches target site at a high concentration | -invasive route of exposure -eye pain, eye inflammation, increased intraocular pressure |
| **Diabetic Retinopathy: Triamcinolone** | | -anti-inflammatory effects as a result of the corticosteroid inhibiting inflammatory programs of gene expression to help with macular edema | -intravitreal injection | -invasive route of exposure -requires highly qualified optimologist |

## CONCLUSION

### ANALYSIS

- Based on recent research there is evidence to suggest that serotonin modulators have neuroprotective potential in animal studies.
- One such modulator, 8-0H-DPAT - a potent 5-HT1A and partial 5-HT7 agonist - decreases depolarization or NMDA mediated Ca2+ influx by opening K+ channels leading to hyperpolarization. This may attenuate neuronal damage by decreasing excitotoxicity neurotransmitter release and / or Ca2+ overload during ischemia.
- Melena, J. et al. 2000 also found that 8-OH-DPAT binds directly to the receptor and prevent Na+ influx into the cell. [3]

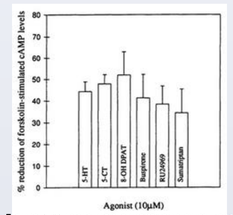


Figure 6. % inhibition of forskolin stimulated cAMP levels with Serotonin agonist treatment. 4

- A preincubation with various Serotonin agonists reduced the ability of forskolin to increase cAMP production, shown in fig 6. This effect involves interaction with retinal 5-HT1A and 5-HT7 receptors, decreasing adenylyl cyclase roduction, reducing cyclic AMP levels, which reduces aqueous humour formation, decreasing intraocular pressure.

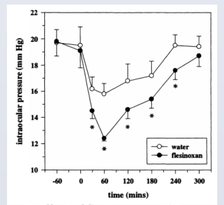


Figure 7. Effect of flesinoxan on IOP

- However, in Phase 3 Clinical Trials, run by Alcon, the agonist AL-8309B proved ineffective and the study was terminated. This trial had 772 participants, given topically twice daily for 30 months. The annual lesion enlargement rate was measured with fundus autofluoresence imaging. It was found that there was no difference in reduction in lesion size in comparison to the control.
- In conclusion, while there is evidence that these serotonin agonists have neuroprotective properties in animal studies, there is no conclusive evidence that they are neuroprotective in human studies.

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