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Soluble Guanylate Cyclase α1–Deficient Mice: a novel murine model for Primary Open Angle Glaucoma

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Background

Glaucoma is an optic neuropathy characterized by retinal ganglion cell degeneration leading to vision loss. Primary open angle glaucoma is a subtype of glaucoma that results in visual field loss due to optic nerve damage caused by increase in intraocular pressure. Events in primary open angle glaucoma (POAG) pathogenesis has been associated with nitric oxide (NO) which activates soluble guanylate cyclase (sGC), a heterodimeric enzyme consisting of α and β subunits by cGMP signaling.1,2 In POAG patients NO metabolites and level of cGMP has been found to be decreased in aqueous humor. Impaired signaling can be a contributing risk factor to the etiology of the POAG.3 However whether signal impairment can result in POAG and mechanism underlying is yet to be elucidated.

In the present work authors have identified a novel murine model to study the pathogenesis of age related optic neuropathy in POAG. Further study was extended to human subjects to explore the role of sGC in POAG pathophysiology in case of humans by performing gene association studies.

Study Design

1 to 17 months old mice deficient in sGC α1+/− and age matched wild type mice were studied for POAG disease development. Female mice were studied to rule out the systemic hypertension that may give confounding effects. To determine the localization of sGC α1+/− and β subunits immunohistochemical studies were carried in mice retinal sections as well as sections of human eyes obtained from New England Eye Bank. sGC α1, and sGC β1 were found to be expressed abundantly at three major site ciliary muscles, smooth muscles of retinal vessels and retinal ganglion cells. The expression in these sites suggested that sGC might change contractility of ciliary muscles, regulates blood flow or viability of RGC. Further to explore the role of sGC in human POAG, association between POAG and genes encoding α and β subunits of sGC was studied by single nucleotide polymorphism analysis in individuals with the disease.

Implications

The present study has demonstrated that deficiency of sGC α1 leads to primary open angle glaucoma in old mice and thus sGC α1+/− mice provide a valuable tool for translational studies for POAG. This novel animal model may further be explored to deduce the mechanism or signal transduction leading to POAG. Genetic analysis studies revealed the relevance of this mouse model in case of humans. It can also be concluded from the present study that sGC is a potential target enzyme to be exploited for POAG therapeutics.

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References

