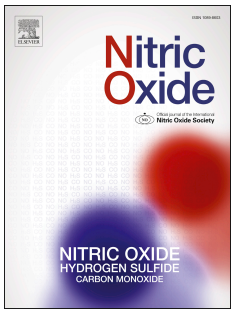
Accepted Manuscript



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PII: S1089-8603(18)30054-5

DOI: 10.1016/j.niox.2018.04.010

Reference: YNIOX 1784

To appear in: *Nitric Oxide*

Received Date: 23 February 2018

Revised Date: 18 April 2018

Accepted Date: 23 April 2018

Please cite this article as: L.K. Wareham, E.S. Buys, R.M. Sappington, The nitric oxide-guanylate cyclase pathway and glaucoma, *Nitric Oxide* (2018), doi: 10.1016/j.niox.2018.04.010.

The Nitric Oxide-Guanylate Cyclase Pathway and Glaucoma

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Abstract

Glaucoma is a prevalent optic neuropathy characterized by the progressive dysfunction and loss of retinal ganglion cells (RGCs) and their optic nerve axons leading to irreversible visual field loss. Multiple risk factors for the disease have been identified, but elevated intraocular pressure (IOP) remains the primary risk factor amenable to treatment. Reducing IOP however does not always prevent glaucomatous neurodegeneration, and many patients progress with the disease despite having IOP in the normal range. There is increasing evidence that nitric oxide (NO) is a direct regulator of IOP and that dysfunction of the NO-Guanylate Cyclase (GC) pathway is associated with glaucoma incidence. NO has shown promise as a novel therapeutic with targeted effects that: 1) lower IOP; 2) increase ocular blood flow; and 3) confer neuroprotection. The various effects of NO in the eye appear to be mediated through the activation of the GC- guanosine 3:5′ -cyclic monophosphate (cGMP) pathway and its effect on downstream targets, such as protein kinases and Ca^{2+} channels. Although NO-donor compounds are promising as therapeutics for IOP regulation, they may not be ideal to harness the neuroprotective potential of NO signaling. Here we review evidence that supports direct targeting of GC as a novel pleiotrophic treatment for the disease, without the need for direct NO application. The identification and targeting of other factors that contribute to glaucoma would be beneficial to patients, particularly those that do not respond well to IOP-dependent interventions.

1. Introduction

Glaucoma is a neurodegenerative disease characterized by progressive degeneration of retinal ganglion cells (RGCs) and subsequent irreversible loss of vision. Over 60.5 million people worldwide are affected by