Seeing is believing: NO therapy for glaucoma? Focus on “Role of nitric oxide in murine conventional outflow physiology”

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Nitric oxide (NO), a highly reactive, naturally occurring biogas in mammals, is critical to regulating vessel health, but it is a potential toxin at high concentrations. NO is produced at modest levels by the synthetic enzyme endothelial NO synthase (eNOS), which resides in all vascular endothelial cells. It is also made by several closely related synthetic enzymes unique to inflammatory and neural cells. In the cardiovascular system, NO plays an important role in suppressing inflammation, platelet activation, and thrombosis, relaxing vasoconstriction in resistance arteries and lowering blood pressure. Data from human cohorts have shown a strong link between loss of NO signaling and cardiovascular, cerebrovascular, renal, and metabolic diseases. This has led to the development and application of NO-targeting therapies to a range of clinical conditions (2).

More recently, the physiological role of NO and its pathophysiological loss have been documented in other disease models. Primary open-angle glaucoma (POAG), a common ocular disorder associated with raised intraocular pressure, affects ~2% of the US population and is the second-leading cause of blindness worldwide due to death of retinal ganglion cells in the optic disk or retinal nerve (5). The mainstay of treatment of POAG include 1) decreasing aqueous humor production through adrenergic receptor modulation or carbonic anhydrase inhibition or 2) accentuating aqueous humor outflow through the trabecular meshwork using cholinomimetics or prostaglandins. Both are incompletely effective. Recent work has suggested that NO and activators of the cytoplasmic NO receptor soluble guanylate cyclase (4) may have beneficial effects and some therapeutic advantages in disease. Ocular hypotensive events equivalent to a reduction in intraocular pressure seen with standard treatments have been demonstrated in response to activation of the NO-cGMP pathway in humans (10). However, the role of eNOS-derived NO in the eye in health and disease is incompletely known. Human studies have demonstrated ciliary muscle and trabecular outflow pathways enriched in eNOS expression (7). Conversely, eNOS polymorphisms have been associated with POAG in certain human populations (1).

In this issue of American Journal of Physiology Cell Physiology, Chang and colleagues (3) provide additional preclinical insight into the role of NO, in general, and endogenous NO, in particular, in controlling ocular aqueous outflow. Employing an elegant whole eye preparation that allowed for controlled perfusion, the authors confirmed that exogenous NO, delivered as the prodrug S-nitroso-N-acetylimid DHM, increased aqueous outflow. Supporting a role for eNOS, eyes from global mutant mice that express human eNOS linked to GFP (eNOS-GFP) and eyes from wild-type mice displayed decreased aqueous outflow following treatment with the peptide cavitratin, which putatively targets caveolin-1 and, thus, should inhibit eNOS. Of some note, eNOS-GFP mutant eyes were more sensitive to the effects of the eNOS inhibitory peptide than were the wild-type eyes. Outflow rates were decreased under several other conditions in eNOS-GFP mutant eyes compared with wild-type eyes. These results raise questions as to the fidelity of the NO signal in the mutant mice that require additional investigation. Also treatment of wild-type eyes with a low concentration (10 μM) of the nonspecific eNOS inhibitor Nω-nitro-L-arginine methyl ester (L-NAME) decreased aqueous outflow, whereas 100 μM L-NAME had no effect on the outflow rate. These multiple unexpected findings may derive from 1) the nature of the ex vivo system employed, as it lacks autonomic neural input, 2) the known threshold effect of exogenous NO (9), 3) differences in NO signaling between wild-type and eNOS-GFP mutant eyes, or 4) yet to be determined nuances in NO signaling within the eye.

It is also not known from the present study if and how eNOS modulates vascular endothelial growth factor (VEGF) signaling in the eye. This is of some relevance, as eNOS, NO, and VEGF are well known to engage in complex cross-talk interactions in other vascular beds. Nonetheless, the work of Chang et al. (3) is novel, as it provides some evidence for a role for endogenous NO as derived from eNOS to alter the aqueous outflow from the eye. This is a step forward in this area, as other reports have evaluated only the effects of excess NO delivered exogenously or pharmacological inhibition of NO signaling on ocular outflow. This study raises several interesting questions regarding the potential translational aspect of NO therapy. Reduction in NO signaling is associated with increasing age (8), a known risk factor for POAG development, while aging populations with glaucoma are at increased risk for subsequent development of cardiovascular disease (6). Furthermore, as NO has been a therapeutic target for some time in patients with cardiovascular diseases, the results of the present work suggest additional studies to determine if patients treated with an NO-targeting therapy for reasons unrelated to eye disease are protected from developing glaucoma or if the use of such agents slows or stabilizes the process once it starts. Such data would provide an impetus for considering manipulation of NO signaling as part of the pharmacological armamentarium for glaucoma.

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DISCLOSURES

J. S. Isenberg serves as Chair of the Scientific Advisory Board of Vasculox, Inc. (St. Louis, MO) and Radiation Control Technologies, Inc. (Jersey City, NJ) and has equity interest in the same. N. M. Rogers has no conflicts of interest, financial or otherwise, to declare.

AUTHOR CONTRIBUTIONS

N.M.R. and J.S.I. drafted the manuscript; N.M.R. and J.S.I. edited and revised the manuscript; N.M.R. and J.S.I. approved the final version of the manuscript.

REFERENCES


