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Annals of Ophthalmology and Visual Sciences

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NO news is good news for eyes: A mini review

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Received: Aug 26, 2018

Accepted: Oct 16, 2018

Published Online: Oct 23, 2018

Journal: Annals of Ophthalmology and Visual Sciences

Publisher: MedDocs Publishers LLC

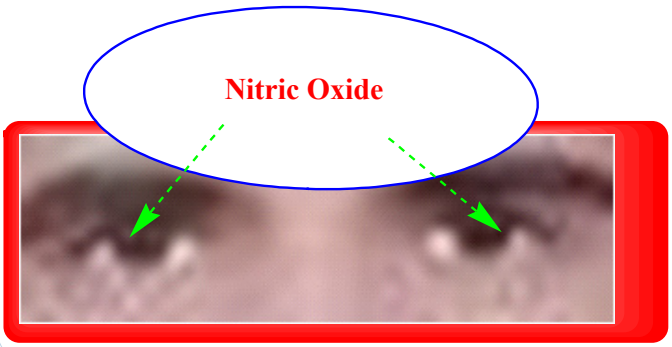
Online edition: http://meddocsonline.org/

Keywords: Gasotransmitters; Nitric Oxide; Eye; Hypertension; Cataract

Abstract

Nitric Oxide (NO) is a well known endogenous gasotransmitter with profound effects on mammalian physiology and also possesses major therapeutic implications. Despite the known toxicity of this molecule when present above the optimal concentration, plays key signaling and regulatory role in human life processes. From the literature survey it is evident that NO bears potential role almost in every system of human body. Among these systems nervous system has also been found linked with this molecule. World scientific community is eager to explore the respective relation in connection with eye physiology. Eye defects are being treated with the NO-releasers and in due course of investigation so many molecular models have been put forth to study their possible use in catering eye problems. Hence herein, a mini literature review is being reported with the biological implications of this molecule in relation to eye physiology and some respective therapeutic aspects. The overall study reveals that a lot is yet to be done to flourish NO-chemical aspects with regard to the exploration of mechanism of NO-action and inventing feasible/biocompatible (eye-compatible) Nitric Oxide Releasing Molecules (NORMS). A number of NO-releasers have been in practice to rectify eye-related health issues. In this context many of the molecules represent practically significant activity. Therefore this mini-review of NO represents good news for eyes.

Graphical Abstract



Cite this article: Mir JM, Maurya RC. NO news is good news for eyes: A mini review. Ann Ophthalmol Vis Sci. 2018; 1: 1003.

Introduction

In 1980 nitric oxide was declared as one of the most important physiological regulators [1,2] that put the whole scientific community in wonder. The key role that this molecule plays in signal transduction and cytotoxicity is counted as one of the biggest surprises in biological chemistry in recent times. The biological scope of this molecule is well pronounced in neuroscience, physiology and immunology. The compliments discovered in biochemical concern of nitric oxide bagged the voteof ''Molecule of the Year'' in 1992 by the journal "Science", published by American Association for the Advancement of Science (AAAS) [3]. In the current times NO is accepted to be associated with numerous physiological pathways including platelet aggregation and adhesion, neurotransmission, synaptic plasticity, vascular permeability, hepatic metabolism, senescence, and renal function [4-7]. At higher (μM) levels, NO also plays key role in host immunity [8] and tumor suppression [9,10]. In 1998 R. F. Furchgott, L. J. Ignarro and F. Murad shared the Nobel Prize for Medicine or Physiology for identifying nitric oxide as a key signaling molecule in cardiovascular system. The importance of this gaseous molecule in the microbial world is advented from NO as an intermediate in denitrification [11] (Figure 1) and is detoxified by pathogens [12,13]. Additionally, the molecule is widely tailored by inorganic and organic chemists in various forms because of its valuable therapeutic potential [14,15].

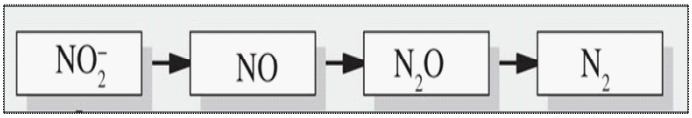


Figure 1: Denitrification involving NO as intermediate

Eye is one of the primary sense organs which are very sensitive. Any defect in eye function needs ultra care and meticulous way of treatment. Among eye health problems Intraocular Pressure (IOP), cataract and retinal hypertension continue to remain as the primary risk factors amenable to treatment. There are numerous evidences supporting eye adaption with Nitric Oxide (NO) connected with the NO-Guanylate Cyclase (GC) pathway. Due to our growing interest towards synthesis and formulation of various NO and CO tagged complexes, the current review focuses on the applied interests of nitric oxide towards the eye-physiology [16-21]. The historical perspective of the evolution of the term "gasotransmitter", endogenous production of NO and seek for efficacious NORMS for eye-treatment are the main over viewed objectives presented in this work.

Concept of ''gasotransmitter''

Signaling molecules in biology may be defined as the special class of compounds known to possess property of transmitting information among cells in human body. The characteristic like size, shape, and function of such molecules varies depending upon the nature of action and target. Some carry signals over short distances, while others transmit information over very long distances (Figure 2). Signaling molecules may be in all sizes and chemical dispositions, ranging from relatively large proteins to gaseous molecules (although in solvated form) [21]. Based on the variations in their properties, signaling molecules are broadly classified as neurotransmitter and gasotransmitter. Neurotransmitters are compounds produced by neurons and stored in vesicles until stimulation of the neurons trigger their release. Specific membrane receptor in a neighboring cell is encountered by the signaling molecules to produce a physiological effect. A number of features are being shared by amine, amino acid and peptide neurotransmitters and are stored in synaptic vesicles, so that desirable proportion of the stores is released, leaving a reserve pool for safety purpose. The release is the consequence of exocytosis, in which the vesicle fuses with the plasma membrane to expel its contents. Inactivation of the phenomeneon occurs by re-uptake of neurotransmitters into the releasing nerve terminal or adjacent glia by enzymatic degradation or by simple diffusion away from the synapse.

Gasotransmitters on the other hand is a sub family of endogenous molecules of gases or gaseous signaling molecules [21,22]. Unlike neurotransmitters they function without receptors because they are freely permeable to cell membranes [23] and are not stored in vesicles, thus they must be rapidly synthesized in response to stimulation. In other words these molecules are produced on demand and consequently consumed for necessary biological action. Hence, neither exocytosis nor any bio-membrane storage is involved for their release. The ability of these molecules to freely enter a cell stems the fact of having no need of receptors or to activate endocytosis to influence a cell. Therefore these features differentiate this class of bio-molecules from neurotransmitters and hence the need of a separate term arouse in the course of explorations meant for bio-transmitting phenomena. Thereafter, a new term of "gasotransmitters" began to be used for these species. The term "gasotransmitter" was first time coined by Rui Wang [24] in 2002. The literature survey indicates the following criteria to be established for categorizing signaling molecules as gasotransmitters:

- Small size
- gaseous molecule (in free state outside a living cell)
- freely permeable to cell membranes
- endogenously and enzymatically produced and regulated,
- and have specific well-defined biological roles at specific concentrations.

The scientific community was thrilled when the final outcome of Endothelium-Derived Relaxing Factor (EDRF), a vasorelaxant, was found to be a gaseous molecule secreted from endothelial cells, [25]. This showed the way to conclude that NO is an endogenous gaseous molecule and was categorized as gasotransmitter, which subsequently triggered the exploration of other possible gasotransmitters, including CO and H2S [26]. With the advent of these small signaling gasotransmitters a new type of science related to endogenously derived gases could elicit crucial biological functions, as well as contribute to the pathogenesis of human diseases [27]. Several other gases are currently under investigation to determine if they too act as endogenous mediators, including acetaldehyde, sulfur dioxide, dinitrogen oxide and ammonia. Overall, these new insights have improved our understanding of biological essence of gasotransmitters not only in physiological functions, but also in the pathogenesis of human diseases.

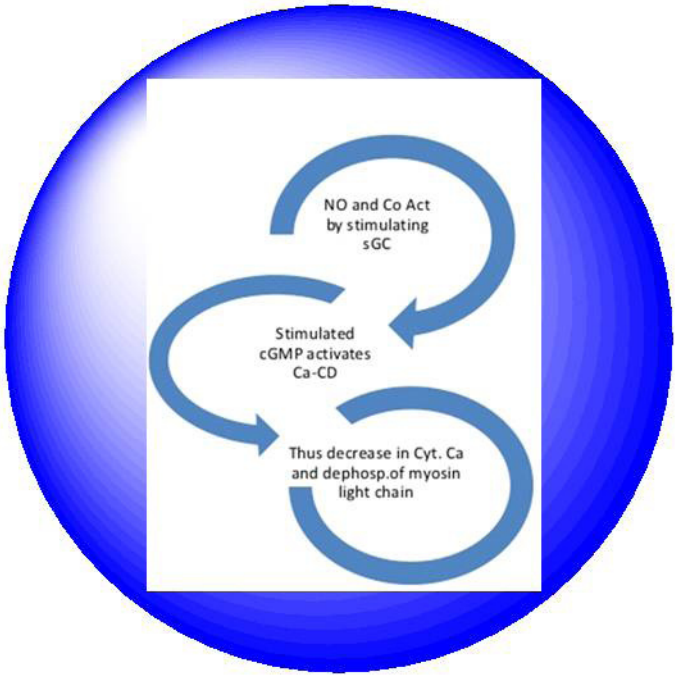


Figure 2: Signaling mechanism

Endogenous production of NO

Nitric Oxide Synthases (NOSs), multi domain hemeprotein enzymes catalyze biosynthesis of NO that specifically involve the oxidation of L-arginine to NG-hydroxy-L-arginine and eventually to L-citrulline and NO [28]. In due course of NO formation, NADPH and molecular oxygen serve as electron sources for oxidation, with three electrons contributed by NADPH and two from O_2. Two successive O_2-dependent mono oxygenation reactions with a stable intermediate,

NG-hydroxy-L-arginine (NHA) intervene during NOS catalytic cycle [29]. It is to mention here that NOS exists in multiple isoforms including neuronal NOS (nNOS or NOS I) [30], inducible NOS (iNOS or NOS II) [31] and endothelial NOS (eNOS or NOS III) [32] differing in the distinct genes that encode them [33]. All the mentioned isoforms produce nitric oxide from oxygen and the guanidine nitrogen of L-arginine (Figure 3).

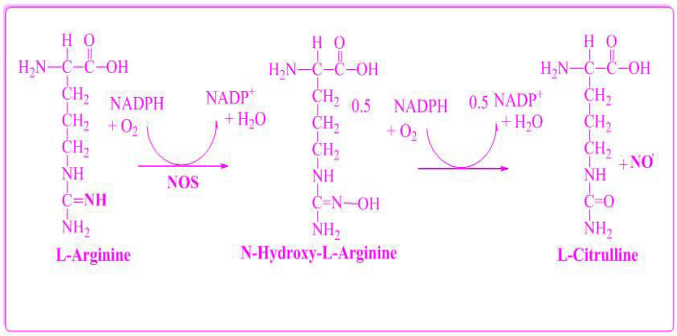


Figure 3: Biosynthesis of NO

Role of nitric oxide in eye

Nitric oxide is found to have precious role in maintaining homeostasis among humans. The role that it plays in sensory neurons triggered the search for its possible concern as homeostatic mediator in the eye. These functional regulations include maintenance of aqueous humor dynamics, neurotransmission of retina and photo-transduction. Any halt in its generation or malfunctioning of the respective metallo-protein actions could result inveitis, retinitis, glaucoma or retinal degeneration [34]. It is now known that endothelial NO synthase (eNOS) and neuronal NOS (nNOS) are activated in normal tissues to produce NO for physiological functioning of eye [35]. The expressions of neuronal and immunologic NOS have been detected in the retina. Different studies reveal that neuronal NOS may be responsible for producing nitric oxide in photoreceptors and bipolar cells. This is followed by stimulation of guanylate cyclase of photoreceptor rod cells and increases calcium channel currents. It has been proven that NOS action if halted In the retina of cats, results in photo transduction impairment [36]. Additionally, Müller cells and in retinal pigment epithelium contains Inducible nitric oxide synthase responsible for keeping normal phagocytosis of the retinal outer segment. Nitric oxide also caters retinal circulation. Very recently, some findings suggest the strong correlation between NO and hypertension associated cataract formation. The elevation of lens nitrite (NO metabolite) is one of the key factors of augmentation of lenticular oxidative stress and cataract formation in the hypertensive condition [37]. Therefore, This reactive, short-lived gas is involved in diverse processes within the retina, and its significance continues to be actively studied [38].

Use of NORMS in the treatment of eye defects

Due to a special enzyme nNOS concerned with neural induction, the eye which is important organ of sensing light or visual sensory system, recently Non-arteritic ischemic optic neuropathy (NAION) has been found to be associated with phosphodiesterase (PDE) inhibitors assumedly due to hypotensive effect and vasodilation, though a causal link has not been established [39,40]. As per a recent study vasodilating agents have been suggested as similar associates of NAION [36]. Similarly in another report the application of valproic acid has been investigated to increase production of NO and expression of eNOS mRNA. Thus, this compound might serve as increaser of aqueous outflow through the trabecular meshwork [41]. Latanoprostene Bunod (LBN) which is a well known topical ophthalmic therapeutic for the reduction of Intraocular Pressure (IOP) in patients with open-angle glaucoma or Ocular Hypertension (OHT) contains Latanoprost Acid (LA) linked to a Nitric Oxide (NO)-donating moiety and is the first NO-releasing prostaglandin analog. This role has been because of its participation in increasing uveoscleral outflow of aqueous humor (AqH). In this connection the recent most findings have indicated the role of NO in the IOP-lowering efficacy of LBN. Hence, confirms the link of NO with eye (Figure 4).

Glaucoma is a common optic neuropathy indicative of progressive dysfunction and loss of retinal ganglion cells (RGCs) and their optic nerve axons leading to irreversible visual loss. So many risk factors have been found responsible for the disease, but increased Intraocular Pressure (IOP) continues to be the primary concern to be treated [19,21]. Reducing IOP though is not always preventive measure of 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: Decrease IOP, elevate ocular blood flow and bestow neuroprotection. Ideally, novel glaucoma therapeutics would target both IOP dependent and -independent mechanisms of the disease [42-44].

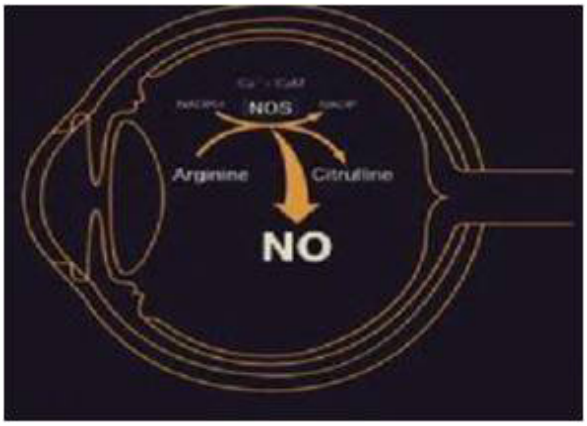


Figure 4: NO-activity inside an eye

Concluding remarks

The main finding that may be culminated from the overall literature survey is hence good news for the eyes. Since, eye is the main optical active organ connected with brain needs ultra care in treating its any malfunctioning state. Due to various unknown facts regarding the applications of NO-releasers in this regard have rendered so many quests yet to be solved. How IOP dependence can be manifested in design of target drugs. Secondly, can the nature of organic to inorganic NO releaser improve the quality of the treatment. In addition to all, the main drawbacks need to be fully addressed of each new NO-releasing molecules to fetch a safe treatment of this organ.

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