Posted on Authorea 23 Nov 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.160614188.83707688/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

The primary gasotransmitters and their respective donors in the mission of vision (eye health): a comprehensive overview

Jan Mir[1] and R Maurya[2]

[1]Islamic University of Science and Technology
[2]RDU Jabalpur

November 23, 2020

Abstract

Nitric oxide (NO) along with Carbon monoxide (CO) and Hydrogen Sulphide (H2S) are biologically significant gaseous molecules generally called as "gasotransmitters". At a concentration higher or lower than optimum value may result in toxicity or malfunctioning of mammalian tissues. Soon after the acknowledgment of NO as multifunctional bio-signalling molecule in 1987, many interesting implications of this field emerged out. Meanwhile, several studies have proven the NO-biosynthetic pathway responsible for normal functioning of eye. High intraocular pressure (IOP) has been suggested as the main risk factor in this context and collaborative approach with nitric oxide releasers is said to control IOP and hence the relation with glaucoma. Similar miracles were reflected from several other naturally produced gaseous molecules,viz., CO and H2S after year 1990. The biological roles of both these molecules are now widely accepted and in the current era investigations focused mainly with development of efficient CO and H2S releasing compounds. CO and H2S donors are also said to help in normalising IOP like NO. Therefore the trio-gasotransmitters have collective relation with the ophthalmic homeostasis in association with nervous control. On one hand, the antimicrobial efficiency of these three molecules is widely known and on the other hand, their collaborative key-role in ocular nerve functioning makes it remarkable to state here that their donors are supposed to act as a shield for both the infectious as well as the non-infectious eye defects.

Data openly available in a public repository that issues datasets with DOIs The data that support the findings of this stu

The primary gasotransmitters and their respective donors in the mission of vision (eye health): a comprehensive overview

J. M. Mir[1,2] and R. C. Maurya[1]

[1*]Coordination, Bioinorganic and Computational Chemistry Laboratory, Department of P.G. Studies and Research in Chemistry and Pharmacy, Rani Durgavati University, Jabalpur, M.P., India, E-mail: mirjanmohammad@gmail.com

[2]Department of Chemistry, Islamic University of Science and Technology, Srinagar (J&K), India,

ABSTRACT

Nitric oxide (NO) along with Carbon monoxide (CO) and Hydrogen Sulphide (H_2S) are biologically significant gaseous molecules generally called as "gasotransmitters". At a concentration higher or lower than optimum value may result in toxicity or malfunctioning of mammalian tissues. Soon after the acknowledgment of NO as multifunctional bio-signalling molecule in 1987, many interesting implications of this field emerged out. Meanwhile, several studies have proven the NO-biosynthetic pathway responsible for normal

Posted on Authorea 23 Nov 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.160614188.83707688/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

functioning of eye. High intraocular pressure (IOP) has been suggested as the main risk factor in this context and collaborative approach with nitric oxide releasers is said to control IOP and hence the relation with glaucoma. Similar miracles were reflected from several other naturally produced gaseous molecules, *viz .,* CO and H_2S after year 1990. The biological roles of both these molecules are now widely accepted and in the current era investigations focused mainly with development of efficient CO and H_2S releasing compounds. CO and H_2S donors are also said to help in normalising IOP like NO. Therefore the trio-gasotransmitters have collective relation with the ophthalmic homeostasis in association with nervous control. On one hand, the antimicrobial efficiency of these three molecules is widely known and on the other hand, their collaborative key-role in ocular nerve functioning makes it remarkable to state here that their donors are supposed to act as a shield for both the infectious as well as the non-infectious eye defects.

Keywords: Gasotransmitters; Ophthalmic diseases; NO; CO; H_2S, NORMs, CORMs, H_2S-donors.

Introduction

The scientific recognition of carbon monoxide (CO) and hydrogen sulphide (H_2S) as bio-conjugated molecules sharing similar functional role as nitric oxide (NO) resultedin coining the term “gasotransmitters” for these molecules based on size, lipophilic character,half-life and several other features [1, 2].Even though these gases share a number of common features, they also possess dissimilar characteristics and display noteworthy interactions, which complicate the interpretation of their physiological activities.

In the late 1990’s, the scientific community saw a very unusual phenomenon, the conversion of nitric oxide from harmful gases into an important chemical messenger. The remarkable role of this molecule in signal transduction and cytotoxicity is considered to be one of the greatest marvels of biological chemistry in recent times. The biological diversity of this molecule is well documented in neuroscience, physiology and immunology [3,4]. Recommendations obtained from the chemical stress of nitric oxide included the ”Molecule of the Year” vote in 1992 by the journal ”Science”, published by the American Association for the Advancement of Science (AAAS) [5]. At present, NO has been accepted to be linked to many physiological mechanisms including platelet aggregation and adhesion, neurotransmission, synaptic plasticity, vascular permeability, hepatic metabolism, senescence, and renal function [6-9]. In high concentration (μM), NO also plays a strategic role in the immune system [10] and in suppression of carcinogenic state [11, 12]. The prominence in the absence of biology and medicine was emphasized in 1998 when the Nobel Prize for Physiology and Medicine was awarded to Robert Furchgott, Louis Ignarro and Ferid Murad for their role in transforming the role of NO in the nervous, cardiovascular and physiological systems. In microbial world NO plays mediator role in denitrification [13-15] (**Figure 1**). In addition, the molecule is tailored in various ways due to its important therapeutic potential [16,17].

NO_2^- NO N_2O N_2

Figure 1 . Denitrification involving NO as intermediate

Carbon monoxide (CO) has long been known as a dangerous gas for mammals and is called as a “silent killer” [18]. Carbon monoxide, when inhaled enters the bloodstream, formscarboxyhaemoglobin (COHb) at a rate 240 times greater than oxygen [19]. This reduces the oxygen transport ability and results in hypoxia [20]. Biologically, CO is considered as a by-product of heme oxygenase (HO) metabolism [21], and in the early stage of its biological exploration, CO was found as a chronic neurotransmitting agent [22]. Therefore, the further studies have altered the general perception of CO as a harmful molecule[23]. CO has now become an important molecule in the physical monitoring of many organ systems. In the last few decades, investigations related to CO have shown this gaseous molecule as a major chemical messenger.

In the seventeenth century, Carl Wilhelm Scheele recognized H_2S through chemical analysis. However, it has long been speculated that the gas is derived from the sewage system, and is linked to a series of special eye diseases that occur in sewage workers. The disease is associated with severe inflammation, secondary bacterial attacks and even blindness [24].Similar to NO and CO, internally generated H_2S is now considered a significant gasotransmitter [25] and within a neuromodulator, which draws a lot of attention in literature.

Posted on Authorea 23 Nov 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.160614188.83707688/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

Traditional neurotransmitters bind to and activate membrane receptors, whereas gasotransmitters are able to freely distribute to adjacent cells and directly bind to their target proteins to supplement biological functions by contributing to their short-term mutations [26].

Like NO which S-nitrosylates a variety of proteins, H_2S physically regulates the different protein functions by S-sulfhydration. However, S-nitrosylation inhibits enzymes, while S-sulfhydration stimulates them. Therefore, H_2S is an important physiologic gasotransmitter such as NO and CO [27-30].

The eye is one of the most sensitive parts of the brain. Any impairment in eye function requires high quality care. Among eye health problems intraocular pressure (IOP), cataract and retinal hypertension continue to remain as potential risk factors in treatment. Due to our growing interest in the synthesis of various chemicals tagged with NO, CO and H_2S [31-39] and the many biological actions of H_2S and the more precise delivery of this flexible gas to target tissue in the form of H_2S sponsors [40], the current chapter focuses on in the applied interest of NO, CO and H_2S-compounds on eye-physiology. A historical view of the emergence of the term "gasotransmitter", within the production of NO, CO and H_2Sin mammals, and to sought strong sponsors of NORMS, CORMS and H_2S-releasers (in the event of chronic biosynthesis and digestion) applicable in the most common eye-defects are the main objectives of thisliterature update.

A Meaningful Introduction Towards "Gasotransmitters"

In general, gasotransmitters refer to the distinctive class of molecules like NO, CO and H_2S, responsible for communication amongstbody cells for a particular biological action. Albeit, these molecules exist in solvated form while in biological medium, the respectivedifferences in size, action, shape and bio-membrane interactions stems their multitude biological roles reported so far. The signal transduction pathway among such carriers may range from short to long distances to transmit the required information[41]. The properties and functional diversity found in these bioessential signalling molecules, therefore gave rise to coin a new term in reference to their biological relevanceas "gasotransmitters".

Several parameters may be found differentiating neurotransmitters from gasotransmitters. From the cellular biology it is clear that neurotransmitters stored in vesicles get released by the intervention of a suitable stimulus (**Figure 2** , top). These responses are receptor-specific in nature and depend on the molecular signalling to bring forth a physiological move. Hence, synaptic vesicles behave as a reservoir of information required at the time of safety or normal physiological functioning. Whereas, gasotransmittersare endogenously availedsmall molecules of signalling potentiality ("gaso" refers to their gaseous nature under normal conditions) [41, 42]. Gasotransmitters have the main characteristic feature of diffusing through cellular membrane without the aid of any receptor (**Figure 2** , bottom). No reservoir is required (like vesicles in neurotransmitters), but are rapidly produced in response to a stimulus when needed[1, 2]. Moreover, here in gasotransmitters cell exocytosis fashion followed in neurotransmitters is not pronounced at al.Therefore a separate term 'gasotransmitter' coined by Wang in 2002 is suitable to distinguish them from neurotransmitters [25].The vasorelaxant and gasotransmitter labelling of NO enhanced scientific vigour to an extraordinary fashion and activated the seek for other molecules of this class [43,44, 25]. [44]. Gases other than these are also under interrogation to add further possible members to this group.

Figure 2. Diagram showing the mechanism of neurotransmitter (2A, top) and gasotransmitter (2B, bottom)action.

Biosynthesisand target of NO, CO and H_2S

Biological synthesis and target of NO

NOis biologically synthesized by the catalytic action (oxidation of the nitrogen coloured red in **Figure 3**) ofnitric oxide synthase (NOS) over L-arginine as substrate and resulting in the formation of L-citrulline [45]as shown in **Figure 3** . Since, the NO production is involved in every system of a human body, there are three distinctive gene products and isoforms of NOS, producing NO in the presence of oxygen, flavins and NADPH [46]. **Figure 4(i)** and**Figure 4(ii)** represent these three members as NOS-I, NOS-II and NOS-II. These are also called as eNOS (endothelial), iNOS (inducible) and nNOS (neural), respectively, because of the specific

Posted on Authorea 23 Nov 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.160614188.83707688/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

target/production locus during their biosynthesis.NOS-I is central and peripheral nervous system linked [47], NOS-III is vaso-relaxationconnected [46] and NOS-II is immunological directed. From the literature it is found that NOS-II functions independent of the presence of calcium, and is a source of considerable amount of NO produced for a longer duration as compared to NOS-I and NOS-III [48].Several examples L-arginine structural analogues have been found to prevent NOS from producing NO,*viz .,* N^G-monomethyl-L-arginine (L-NMMA), N^G-nitro-L-arginine (LNA), N^G-nitro-L-arginine methyl ester (L-NAME), etc. [49]. However, by making instant and sufficient arginine availability, the action could get reversed initially.

Figure3. Reaction showing thebiosynthesis of nitric oxide

Figure4. Interaction of three NOS isoforms

Biological Production and Target of CO As per the metabolic pathways concerned with the CO-biosynthesis, almost 14% of 500 µmol/day is obtained from lipid peroxidation and from photooxidation plus self-activation of cytochrome p-450. Bacteria and Xenobiotics also contribute the same minor percentage [67,68]. Major contribution(almost 86%) is generated by the erythrocyte-breakdown, wherein, the haem-oxygenase (HO) catalyzes this oxidation. Like NOS, HO also exists in two isoforms,*viz,* HO-1 and HO-2. These are alsocalled as inducible and constitutive,respectively. Both the isoforms show same rate-limiting step while catabolizing heme, the difference lies with the regulation, amino acid sequence, and distribution in the tissues. Another HO has been recently identified and named as HO-3. This form of HO was detected in the several organs of rats. Till date no haem-degradation study has been reported for this newly detected HO-member [69].The metabolic pathwayof HO-catalyzed haem oxidation involves several important stages as has been illustrated in **Figure 5** . In addition to CO other intermediatory products like of α-meso-hydroxyheme, verdoheme, biliverdin (converts to bilirubin as excretory product conjugated by glucoronic acid shown in**Figure 6**) are also involved. [70,71].The bioaction of HO-1 under stressful situation gets enhanced and the CO-production gets increased than the optimal value [72]. Therefore, suchan elevation in the concentration can be used as a sign convention medically to read the associated behaviour. The similar correlation has been found in several diseases wherein a patient is expected to suffer from stress and strain conditions.For instance in bronchiectasis,asthma, cystic fibrosis, hyperglycemia and other diseases CO level appears higher than the normal [73]. Hence, the detection level of CO because of inducible HO-1 can help in diagnosis of pathophysiological state.

Figure 5. Oxidation of heme by heme oxygenase (HO)forming CO as a by-product.

Figure 6. Chemical structure ofGlucuronic acid

CO in mammals has been found to show target specific action in two ways,*viz.* ,soluble guanylyl cyclase (sGC) pathway and Non-cGMP pathways. It is well established fact that NO binds with heme by replacing one histidine unit to result in the activation of soluble guanylyl cyclase (sGC) [74]. Generally NO binds to heme b to formaunstable short lived six-coordinate systemto finally cleave the heme-His105 bond, and forms a five coordinated heme complex with NO (**Figure 7**). Therefore, it is conformational change in other words that leadsto sGC activation [75].The resulting sGC catalyzes the conversion of GTP to cGMP in the fashion as given in**Scheme-1.** The cGMP formation is related to a number of sequential pathways entailed with several clinical implications asillustrated in**Scheme-2** (red coloured).

Figure.7 . Diagram showing the activation of guanylyl cyclase by NO and CO/YC-1.[Taken from Ref. E. Martin, K. Czarnecki, V. Jayaraman, F. Murad and

J. Kincaid, *J. Am. Chem. Soc.*, 127(2005) 4625-4631]

Scheme-1: sGC catalyzing the Conversion of GTP tocGMP

Scheme-2: Cyclic guanosine monophosphate (cGMP)routes ameliorating medical conditions shown as red.cGKs = cGMP-dependent protein kinases, Iα and Iβ· IRAG =Inositol 1,4,5-triphosphate(IP_3)receptor-associated cGKIβ substrate; VASP = vasodilator-stimulated phosphoprotein; PDEs =phosphodiesterases;

Posted on Authorea 23 Nov 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.160614188.83707688/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

cAMP = cyclic adenosine monophosphate [Adopted from Ref. Brian E. Mann and Roberto Motterlini, Chem. Commun., (2007) 4197-4208]

Therefore, in an analogous way like NO, this molecule (CO) alsoyields cGMP by activating guanylyl cyclase. However, it may be mentioned here that this activation is only $1/80^{th}$effective as NO. Some trials have been found to use synthetic compounds like YC-1 (**Figure 8**), when used in combination with CO can increase this effectiveness up to the level of NO. This indicates that there should be some naturally existing signalling molecule like YC-1 that shows the guanyl cyclase activation similar to NO.There are contrary observations reported for CO-activity in the same activation study. CO while coordinating withguanylyl cyclase results in six-coordinated iron complex and central metal ion continues to remain as Fe^{II}. The retention of five-coordinated inability of CO with iron is due to the increased radii of the ion anddecrease in the electronegativity. This shows CO-based vasorelaxation goes through a no similar pathway as in NO. On the other hand, considering YC-1 interaction with the displacement of His-105 produces a 5-coordinate complex with retaining CO as co-ligand [79](**Figure8**),there is another interpretation for the CO-dependent stimulation of sGC [80].

Figure 8. Structure of YC-1:1-Benzyl-3-(5'-hydroxymethyl-2furyl)indazole

Non-cGMP CO-pathway is remarkably in other targets to lead vasorelaxation, incorporating the involvement of potassium channels (BK_{Ca}). The conductance BK_{Ca}channels are found distributed almost in everytissue, and get affected byseveral modulators. Among contributing factors towards such channels, protein kinases, endogenous NO and CO along with heme are mentionable. Many physiological processes including neuronal excitability, contractility of muscles, and vascular tone maintenance are because of BK_{Ca} activity by involving the suitable yield of action potential [81].

Biosynthesis and target sites of H_2S

H_2S is considered as the recently recognized third member among gasotransmitters. This gas is also produced endogenously through enzymatic reactions (**Figure 9**) and is responsible for maintaining physiological balance.Recently, non-enzymatic pathways have also been reported to be responsible for biosynthesis of hydrogen sulphide. The optimal concentration of H_2S under normal conditions is said to be present in micromoles (μM) [82].L-cysteine is the important bioessential source of this gas involving the role of cystathionine β-synthase (CBS), cytosolic/pyridoxal-5'-phosphate (P5P)-dependent enzymes, and cystathionineγ-lyase (CSE)[83,84] or the tandem enzymes, cysteine aminotransferase (CAT) and 3-mercaptopyruvate sulphur transferase (3-MST), mainly confining the activity in mitochondria. Absolute H_2S is produced from CSE and CBS, whereas 3-mercaptopyruvate transfers sulphur to cysteine through the catalytic application of 3-MST resulting in the formation of persulfide [85, 86]. Thereafter, persulfide acts as a H_2S-releaser endogenouslycausing the reduction of disulfides,e.g, reduction of dihydrolipoic acid (DHLA) or thioredoxin(Trx) under physiological terms [87]. Strictly, therefore it is thioredoxin reductase (TR) acting sequence wise in combination with glutathione (GSH) and sulfur oxidase (SO) in this phenomenon. The significance of H_2S (oxidized form) in respiratory chain is well documented acting as electron donor in Q,III and IV steps of the chain that results in the generation of energy currency (ATP) and cellular oxygenconsumption. Hence, biosynthesis and H_2S-mediated sensing of oxygen represent essential role of H_2S-biochemistry.

Production of H_2S in tissues via cystosolic enzymes CBS and CSE

(ii) (a) Generation of H_2S via tandem enzymes, CAT and (3-MST) and(b)

H_2S oxidation in the mitochondria

Figure 9. Biosynthesis of H_2S and its oxidation [Adopted from Ref. K. R. Olsona, J. A. Donald, R. A. Dombkowski and S. F. Perry, *Respiratory Physiology & Neurobiology* ,184 (2012) 117– 129]

The biological synthesis of H_2S as in the case of NO and CO, must be followed by the consumption or target phenomenon. This gas has no colour, flammable and smellslike that of rotten eggs.Itsacid strengthis weak (pKa value of 6.98 at 25 °C and 6.76 at 37 °C). The dissociation of this gas in water may be represented as

Posted on Authorea 23 Nov 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.160614188.83707688/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

shown in Scheme-3 (Ka_1=1.3×10^{-7} M, Ka_2 =1x10^{-19}) [39]. The H_2S that remains undissociated is volatile, while the dissociated form HS^- is not volatile. In physiological medium these dissociation patterns are pH-dependant.At the 7.4 pH, one-third of H_2S remains udissociated. Physiological pH does not support the substantial presence of S^{2-}(because high pH is required for it). As per another scientific observation H_2Smainly persists in HS^-form(82%) because of having weak acid strength (pKa_1: 6.76; pKa_2: 19.6)[97].

Scheme-3. Reactions showing the dissociation of H_2S in aqueous solution

Therefore, both the H_2S as well as $SH^-$are contributoryunder biological activity of hydrogen sulfide, despite the fact that SH^-, represents more nucleophilic potential than cysteine (Cys) or reduced form of glutathione (GSH), thatswiftly coordinates with bio-metallic centres or interacts with othercompounds[98].In mitochondrial chain reactions, H_2Sdisplays sequential oxidation trend. Initially, it gets oxidized to thiosulfate, followedby conversion to sulfite and subsequently to sulfate. The first oxidation stage isnon-enzymatic in nature, while the rest steps are carried out enzymatically using thiosulfate cyanide sulfurtransferase (TST). Despite the observation showing sulfate as major end product of the metabolic pathways followed by H_2S, urinary thiosulfate represents a non-specific indicator to sense thequantity of H_2S production within a body [99]. Overall, the target of H_2S is highly influenced by several factors especially the rapid oxidation disfavouring the long-distance transport. Therefore the development of efficient storage system endogenously applicable is suggested.For instance,in NO-association,H_2S gets stored as nitrosothiols(RS-NO) implying the dual gas-combinatory fashion. This opens several areas of interest to seek answer for the unexplored queries regarding the isolated and combined gasotransmitters research.Meanwhile, the solvated fashion of H_2S reveals different solubility trend based on the nature of the solvent. Due to lipophilic feature of this gas, H_2Seasily crosses cell membrane. The tested solubility experiments have shown itto be five times moresoluble in lipophilic solvent as compared to water. The data furnished from its solubility behaviour in various solvents other than water have been keenly recorded [100, 101].The solution chemistry on further exploration depicts that concentration H_2S under varied physiological abnormalities within mammalian blood. Harmful implications of H_2S at the level of <100 ppm gets expressed in the formsore throat, eye irritation, dizziness, etc [102–104].The exposure at greater than 1000 ppm affects CNS, respiratory chain and may more even cause death[104].

Gasotransmitters in the Mission of Vision (Eye-Health Contribution) Eye is one of the most important sense organs performing the function of vision through interacting with light, involving several physicochemical phenomena to memorize the surroundings, and therefore acts as a natural perception mediator to translate the observations to the brain. So, ultimately light-phenomenon to nerve actions, so many tissues collaborate to let such a complex process to happen. The physiology of eye is not restricted to a simple conduction process only, but is subjected to the role of the gasotransmitters introduced*vide supra* . This section details the role of NO, CO and H_2S in maintaining a healthy eye, so is the title established as "the aim of gasotransmitters in the mission of vision".

NO News is Good News for Eyes: NO Donors for the Treatment of Eye Diseases

Since the dawn of NO-recognition as a key signalling molecule, the diversified biological role of this free radical met with its extended role in so many areas of physiological investigations. Keeping in view the combinatory functional status of NO and cGMP are entailed with a range of biological actions, there are numerous evidencessupporting the fact that the NO-metabolic pathways are also involved in the normal functioning of an eye.The respective neurological role served as a motivational move for the researchers to find the possible responsiveness while studyingeye functioning. These responsible roles include dynamics of aqueous humour (AqH) dynamics, retinal neurotransmission and other light induced pathways. Any malfunctioning that results in the respective NO-generation can cause eye abnormality [48]. As of now, the normal tissue functioning of eye in concern with eNOS and nNOSbasedrolehas got wide acceptance [105]. This is because neural and immunologic expressive forms of NOS have been found in retina. Several reports are evidential in supporting nNOSresponsible in photoreception via NO-generation, and similar effect in bipolar cells. This in turn leads to stimulus for guanylate cyclase photosensitive rod cells and thereby increasing the calcium channel activation. By stopping NOS action in the retina of cats, results indicate impairment in photo-transduction [106]. Moreover, iNOS has also been found responsible for keeping normal

Posted on Authorea 23 Nov 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.160614188.83707688/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

phagocytosis in the outer section of retina. Also, the role that NO plays in maintaining circulation of retina, links the molecule with ophthalmologic role.

The optimal concentration as discussed in the biosynthesis is always mainly eyed to confirm the normal functioning of any tissue. At the concentrations other than optimum value results in so many eye diseases [105]. In case of low NO-concentration (eNOS or nNOS abnormal functioning) substances that could act as NO-donors could be administered. On the other side, iNOS as pointed in the above sections isonly intervening in pathological conditions expressive in terms of several cytokines (interleukin-1, interleukin-6, etc), inflammation and endotoxins. Once initiated, iNOS continues to produce sufficient NO followed by conversion phenomenon free radicals, nitrogen dioxide or nitrites as defensive way against pathogens.In hyperactivity of iNOS in several disorders like cataracts, age-related macular degeneration (AMD), myopia and uveitis, iNOS inhibitioncould be suggested.

As is widely known that blood pressure plays important role in keeping normal eye-sight, and on the other hand NO is also considered as blood pressure regulator. Under such a stemming fact, some recent studies have foundeffectivemutual relationof NO with hypertension based cataracts. The increase in lens nitrite (as NO metabolite) is suggested as one of the key regulator for toincrease oxidative stress of lenticular part and hypertensive cataract formation [107]. Thus, NOinvolvement in retinal action continues to be of significant interest [108]. Let us specify this role by illustrating the role of NO in eye defects as elaborated below figures (**Figure 10-figure 13**): [Adopted from L. K. Wareham1, E. S. Buys and R. M. Sappington, The Nitric Oxide-Guanylate Cyclase Pathway and Glaucoma, *Nitric Oxide* , 77(2018) 75–87, Ref. 111].

Hosted file

`image14.emf` available at https://authorea.com/users/378090/articles/494657-the-primary-gasotransmitters-and-their-respective-donors-in-the-mission-of-vision-eye-health-a-comprehensive-overview

Figure10. Diagrammatic representation of aqueous humour (AqH) equality. (a) AqHat the ciliary body in the eye flows (**green arrows**) through two routesindependently that control AqH dynamics: (i) via the trabecular meshwork (TM) and Schlemm's canal (**purple arrow**) (conventional route) and (ii) via the uveoscleral tract (**orange arrow**)(non-conventional route). (b) The balance of (AqH) production at the ciliary body and elimination in the anterior chamber establishes intraocular pressure (IOP) in the eye.

Hosted file

`image15.emf` available at https://authorea.com/users/378090/articles/494657-the-primary-gasotransmitters-and-their-respective-donors-in-the-mission-of-vision-eye-health-a-comprehensive-overview

Figure 11. The NO-GC-1-cGMP pathway, steps in the way of IOP lowering. (a) NO is generated fromL-arginine by nitric oxide synthase (NOS) available in three isoforms: (i) neuronal NOS-I (nNOS), (ii) endothelial NOS-III (eNOS) and (iii) inducible NOS-II (iNOS).(b) NO binds guanylate cyclase-1 (GC-1), a heterodimeric protein capable of converting guanosine 5'-monophosphate (5'GMP) to cyclic guanosine monophosphate (cGMP). The cGMP so produced can target cGMP-gated ion channels, and activate kinase signaling cascades. (c) Phosphodiesterase enzymes (PDEs) bind to cGMP and catalyse the decomposition of cGMP into 5'GMP. PDEs act as important regulators of signal transduction mediated by cGMP. (d) The cGMP bioavailability in the cell can be increased in two ways: (i) by the use of GC-1 stimulators and activators, which increase production of cGMP, or, (ii) by the use of PDE inhibitors that prevent the decomposition of cGMP in the cell.

Hosted file

`image16.emf` available at https://authorea.com/users/378090/articles/494657-the-primary-gasotransmitters-and-their-respective-donors-in-the-mission-of-vision-eye-health-a-comprehensive-overview

Posted on Authorea 23 Nov 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.160614188.83707688/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

Figure12. cGMP-assisted modification of IOP via increase in aqueous humour (AqH) outflow.(a) Nitric oxideactivates generation of cGMP by GC-1. The cGMP activates protein kinase G (PKG). The PKG so activated can phosphorylate numerous targets with various downstream effects, including inhibition of Ras homolog family member A (RhoA).This prevents inhibition of myosin phosphatase by Rho Kinase. (b) Besides inhibition of RhoA, activated PKG can directly trigger myosin light chain phosphatase (MLCP). Thereafter, dephosphorylation of the regulatory light chain of myosin by MLCP prevents actin–myosin interaction, promoting cell relaxation. (c) This, then leads to a widening of the intercellular spaces in the juxtacanalicular trabecular meshwork (TM) and Schlemm's canal.This facilitates conventional AqH outflow and thereby lowering IOP.

Hosted file

`image17.emf` available at https://authorea.com/users/378090/articles/494657-the-primary-gasotransmitters-and-their-respective-donors-in-the-mission-of-vision-eye-health-a-comprehensive-overview

.

Figure 13. GC-1-directed therapy for glaucoma is pleiotropic in its action.Increased levels of cGMP are shown to have pleiotropic targets that are beneficial in the treatment of glaucoma. These are: (a) relaxation of the trabecular meshwork to increase AqHoutflow facility,which leads to lowering in IOP,(b) increasing blood flow to the retina, choroid and optic nerve head, (c) prevention of degeneration of retinal ganglion cells through mechanisms that may involve downstream kinase pathways. As shown in **Figure 11** , the cGMP concentrations in the eye can be increased in two ways: (i) by the use of GC-1 stimulators and activators, which aim to increase production of cGMP; or (ii) by the use of PDE inhibitors which prevent the decomposition of cGMP into 5'GMPin the cell to increase its bioavailability.

The clinical investigations revealthat glaucoma is associated with increased IOP. In case of open angle glaucoma (OAG), the finding of high IOP suggests imbalance between AqH generation and outflow. It is estimated that more than sixty million people suffer from primary open angle glaucoma (POAG) at the world level, showing a possible graphic projection of about seventy nine million by the end of 2020 and more than hundred million by 2040 [109,110]. The general form of glaucoma is indicative ofhigh intraocular pressure (IOP) and hence is known asocular hypertension. From the available data it is clear that 1/3rd of glaucomatous patients (vision loss)show normotensive IOP (normotensive glaucoma; NTG) and this disease have major impact of age factor i.e., increases with age, with impendent of IOP. This shows that this mechanistic approach is not the sole explanation of the cause of this defect [111]. Thus, considering reduction in IOP is not the whole treatment for this disease. Hence, a number of evidences support NO as an efficient regulator of this type of hypertension in association with guanylate cyclase (GC). NO as a therapeutic option for this treatment has shown positive results indecreasing IOP, stabilize ocular blood pressure and confer neuroprotection. Therefore, current therapeutics considers both IOP-dependent and IOP-independent targetmechanisms of the disease [112-114].

Nitric Oxide Releasing Molecules (NORMS) and the IOP

Several NORMS have been tested in animal models including mice, monkey and rabbit to record the impact of these NO-donors on IOP.In case of a normotensive rabbit animal model, theapplication of nitroglycerin, Sodium nitroprusside (SNP), isosorbide dinitrate (ISDN) and sodium nitrite (**Figure14)** showed a suitable decrease in IOP effective for one to two hours. The concentration dependent analysis showed that SNP and nitroglycerin or glyceryl trinitrate(GTN) are active at lowering the IOP till 0.1% and 0.03%, respectively is maintained, and on the other hand doses higher than 0.1% and 0.03% of the two NO-donors were found ineffective [115]. Similarly, other studies reported by Kotikoski *et al* . [116] in normotensive rabbits using SNP, spermine NONOate and S-nitrosothiol (**Figure 15**), applied topically or intravitreal way showed similar effect of lowering IOP for 2-5 h duration. Behar-Cohen's group also reported the similar type of investigation using 3-morpholinosydnonimine (SIN-1) or S-nitro-N-acetylpenicillamine (SNAP), (**Figure 16)** and the results indicated a swift fall in IOP [117].

Posted on Authorea 23 Nov 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.160614188.83707688/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

Figure14. Structure of some nitric oxide donors

Figure 15. Chemical structure ofspermine NONOate

Figure 16. Chemical Structure of SIN-1 and SNAP

The Studies reported bySugiyama*et al.* [118] showing the hypotensive outcome of compounds shown in**Figure 17** encompassing both the NO-releasing and NO-sequestering sensitivity. Kimura*et al.* [119] found that SNP and nipradilol reduce IOP, but latanoprost (**Figure 18)** was found not so effective IOP. However, the combinatory drug application of latanoprost with SNPor nipradilol showedconsiderable reduction in IOP than SNPor nipradilol when used separately. This proposes the use of synergistic effective compound like latanoprost for well pronounced IOP lowering results.

Figure 17. Chemical structure of nipradiol

Figure 18. Chemicalstructure of latanoprost

Non-arteritic anterior ischemic optic neuropathy (NAION), a common eye problem generally found middle-aged group (though no age group is safe) is linked with phosphodiesterase (PDE) inhibitors (such as-Sildenafil)presumably due to hypotensive effect and vasorelaxation [120]. Hence, sildenafil (a well known NORM)finds the application inlowering the blood pressure [121]. Several recent reports describe the use of erectile dysfunction (ED)drugs (**Figure 19**)questioning these drugs as responsible agents forNAION. Many factors have been elaborated to set this beliefof contribution towards NAION. Therefore, among warning factors such possibilities of side effects must be highlighted [122].As the same vision defects have been found among patients aftersildenafil consumption [123]. It is established that PDE 5 (phosphodiesterase in the corpus cavernosum) along getsinhibitedby using the ED drugs, escaping degradation of 3'-5'-cyclic guanosine monophosphate (cGMP) to guanosine 5'-monophosphate (5'GMP).The NO linkage with guanylyl cyclase creates conformational modification in this enzyme, followed by catalytic cGMP generation from guanosine 5'-triphosphate (GTP), stimulating penis towards erection as has been displayed in **Figure 20** .

Figure 19. Structure of sildenafil andother similar ED drugs

Figure 20. NO–cGMP routes for relaxation of arterial and trabecular smooth muscle

Another familiar example of NO-donor usable in lowering IOP is NO-bonded Latanoprost acid (LA) called as Latanoprostene bunod (LBN) and is generally referred for topical treatment, and its action of releasing NO is prostaglandin equivalent. The role of this compound inoutflow of AqH has been described in **Figure10** and the mechanism of NO-release is given in**Figure 21.**

Figure 21. The release of nitric oxide from LBN [Adopted from Ref. 124; *J. Ocul. Pharma. and Therap.*, 34(2018) 52-60].

Carbon monoxide, CORMS and the ocular system

Glaucoma as discussed earlier is an optic neuropathy and is considered as the major cause of eye defectsin advanced countries (125-131). A sequential treatment plan has been devised by the "European Glaucoma Society"suggesting the reduction of IOP as the first step, followed by medically supervised laser surgery of neural network called as "the trabecular meshwork" (TM) andfiltering surgery of galucoma. As the main threat for glaucoma is elevated IOP, hence is thefirst target to be corrected in the treatment plan [134]. Meanwhile CO is also expected to play a role in lowering IOP like NO. Although very less literature reports are available justifying the use of CORMS in this context. However, some of the directions imposed for this view have been enlightened below:

Bucolo and Drago have recently updatedthat CO can furnish significant results of multiscale applications in treating eye impairments especially glaucoma [131].CORM-3 as shown in **Figure 22** is a famous CO-releaser when studied by Stagni et al. To find the role of CO in treating ocular system defects found that the compound resulted in lowering IOP in the rabbit animal models they selected for the experiment [135].The

Posted on Authorea 23 Nov 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.160614188.83707688/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

drug potency in the respective tests indicated that after 24 hours of the consumption the IOP-lowering effect was seen for 30 minutes.Ingestion1% dose was seen maximal six hour duration.

Figure 22. Chemical structure of CORM-3

From the results obtained by CO-based IOP-lowering it is expected that the action is because of soluble guanylyl cyclase(sGC)enhancement. CO-dependent sGC activation of sGC by CORM-3imparts an increase in the outflow of AqH as given in **Figure 23**,linkingthepathways, TM with Schlemm's canal. It is expected that CO exhibits this action byreducing the volume of TM cell [136].

Hosted file

`image27.emf` available at https://authorea.com/users/378090/articles/494657-the-primary-gasotransmitters-and-their-respective-donors-in-the-mission-of-vision-eye-health-a-comprehensive-overview

Figure 23. Diagram displaying theproduction andflow of aqueous humour (AqH). (a) AqHproduced at the ciliary body in the eye flows (**green arrows**) through two routes independently that control AqH dynamics: (i) via the trabecular meshwork (TM) and Schlemm's canal (**purple arrow**) (conventional route) and (ii) via the uveoscleral tract (**orange arrow**)(non-conventional route). (b) The balance of (AqH) production at the ciliary body and elimination in the anterior chamber establishes intraocular pressure (IOP) in the eye. The yearlyrate of incidenceof uveitis (a sight-threatening inflammatory disease of the eye)at the age between 20 and 60 years for both males and females is estimatedto be with a frequency of 38–714 per 1,00,000 persons [137]. CORM-A1 is an example of CO-releasing compounds tested for its effect on uveoretinitis and is the first example of water soluble CO-releaser. **Figure 24**and**Scheme 4**may be referred for knowing the structural details and CO-releasing process.Nicoletti et al. [138] showed that CORM-A1is helpful in autoimmune responsive in uveoretinitis.

Figure 24. Chemical structure of CORM-A1

Scheme 4. Mechanism of CO release fromCORM-A1

Hydrogen Sulphide and ophthalmic Diseases

Being third latest member of gasotransmitters after NO and CO, H_2S has also been reported to exhibit-numerous roles in maintaining normal physiological conditions [139].The generation of H_2S as discussed in its biosynthesis section mainly involves the catalytic intervention of CBS, 3MST, CSE and CAT. The same enzymatic actions have been found operational in all mammalian eyeballs confined to several locations. Any irregularity in such a distribution results in eye defects. So many investigations have been reported detailing H_2S donors as IOP regulating compounds, retinal cell protection, antioxidative stress and ocular protein modulation. Thus, H_2S donors represent promising drugs applicable in treating manifold ophthalmic diseases as discussed below:

Among different factors responsible for ocular defects as is known IOP is the main reason for glaucoma neuropathy [140] and finally it is stability between AqH of ciliary body and outflow AqH that matters [141].By facilitating cyclic adenosine monophosphate (cAMP) the outflow could be enhanced [142]. By allowing H_2S-donors like L-Cysteine and sodium hydrosulfide (NaHS)to act on adenylyl cyclase and ATP-sensitivepotassium channels (K_{ATP}) therefore could increase cAMP concentrations and could make the out-flow ofAqH easy [143].Similar investigation conducted by Modis*et al.* reveals that H_2S inhibits phosphodi-esterase (PDE) and enriches intramitochondrial cAMP levels and results in the excitation of protein kinase A (PKA) to infusebioenergetic consequences [144]. Similarly, another compoundGYY4137 [**Figure 25**] has furnished positive results in stabilizing IOP[145, 146].

Figure 30: Chemical structure of GYY4137

Concluding Remarks and Future Outlook

Posted on Authorea 23 Nov 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.160614188.83707688/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

Gasotransmitters are, therefore, outstanding molecules having significant biological signalling role. Considering the fact that the scientific world is eager to design and develop molecular scaffolds in this context to be declared as medical or clinical relevant, so many questions are underway to be resolved. Half-life period, solubility, chemical environment effects, pH, thermodynamics and kinetics, all are among the queries being investigated in this field.The ocular diseases and the factors responsible for such impairments do contain mechanistic pathways half answered in relevance with gasotransmitters. Drug delivery challenges, transportation, combinatory implications of drugs, optoelectronic effects, etc. need to be explored in a more deepened way. Moreover, could synthetic chemists bring forth a molecular system of synergetic effect in a view to declare molecular designs having potentiality of releasing more than one 'gasotransmitter'molecules?

References

1. R. Wang, (2004) Signal transduction and the gasotransmitters: NO, CO, and H_2S in biology and medicine, Humana, Totowa (2004).
2. P. K.Allan and R. E. Morris, Medical Applications of Solid Nitrosyl Complexes, in "Nitrosyl Complexes in Inorganic Chemistry, Biochemistry and Medicine II, D. M. P. Mingos (Ed.), 154 Structure and Bonding, Springer, Springer-Verlag Berlin Heidelberg (2014).
3. L. J. Ignarro, Endothelium-derived nitric oxide: Pharmacology and relationship to the actions of organic nitrate esters,*Pharmacol. Res.* , 6, 651–659, 1989.
4. L. J. Ignarro, G. M. Buga, K.S. Wood, R. E. Byrns and G. Chaudhuri, Endothelium-derived relaxing factor produced and released from artery and vein is nitric oxide, *Proc. Natl. Acad. Sci. U.S.A.* , 84, 9265–9269, 1987.
5. D. E. Koshland, The molecule of the year, Science, 258(1992) 1861; J. S. Stamler, D. J. Singel and J. Loscalzo, Biochemistry of nitric oxide and its redox-activated forms, *Science* , 258(1992) 1898-1902.
6. L. J. Ignarro, Ed., Nitric Oxide: Biology and Pathobiology, Academic Press, San Diego (2000).
7. A. R. Butler and R. Nicholson, Life, Death and Nitric Oxide, The Royal Society of Chemistry, Cambridge, UK (2003).
8. S. Kalsner, Ed., Nitric Oxide and Free radicals in Peripheral Neurotransmission, Birkhauser, Boston, MA (2000).
9. S. R. Vincent, Nitric oxide neurons and neurotransmission.*Progress in Neurobiology* , 90(2010) 246-255.
10. F. C. Fang, Ed., Nitric Oxide and Infection, Kluwer Academic/Plenum Publishers: New York (1999).
11. S. Moncada, E. A. Higgs and G. Bagetta, Eds., Nitric Oxide and Cell Proliferation, Differentiation and Death, Portland Press, London (1998).
12. A. J. Burke, F. J. Sullivan, F. J. Giles and S. A. Glynn, The yin and yang of nitric oxide in cancer progression,*Carcinogenesis* , 34 (2013) 503-512.
13. J. O. Lundberg, E. Weitzberg , J. A. Cole, N. Benjamin, Nitrate, bacteria and human health, *Nat. Rev. Microbiol* ., 2 (2004) 593-602.
14. L. A. H. Bowman, S. McLean, R. K. Poole, J. Fukuto, The diversity of microbial responses to nitric oxide and agents of nitrosative stress close cousins but not identical twins,*Advances in Microbial Physiology* , 59 (2011) 135-219.
15. F. C. Fang, Antimicrobial reactive oxygen and nitrogen species: Concepts and controversies,*Nat. Rev. Microbiol.* , 2 (2004) 820-832.
16. G. M. King and C. F. Weber, Distribution, diversity and ecology of aerobic CO-oxidizing bacteria,*Nat. Rev. Microbiol* ., 5(2007) 107-118.
17. R. C. Maurya and J. M. Mir, Medicinal industrial and environmental relevance of metal nitrosyl complexes: A review,*Int. J. Sci. Eng. Res* ., 5 (2014) 305-320.
18. L. Wu and R. Wang, Carbon monoxide: endogenous production, physiological functions, and pharmacological applications,*Pharmacological Reviews* , 57 (2005) 585-630.
19. C. G. Douglas, J. S. Haldane and J. B. Haldane, The laws of combination of haemoglobin with carbon monoxide and oxygen, *The Journal of Physiology* , 44 (1912) 275-304; J. B. S. Haldane, Carbon monoxide as a tissue poison, *Biochemical Journal* , 21 (1927) 1068-1075.
20. L. K. Weaver, Carbon monoxide poisoning, *Crit. Care Clin* ., 15 (1999) 297-317; D. Gorman, A.

Posted on Authorea 23 Nov 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.160614188.83707688/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

Drewry, Y. L. Huang and C. Sames, The clinical toxicology of carbon monoxide, *Toxicology* , 187 (2003) 25-38.
21. T. Sjostrand, Early studies of CO production, *Ann. NY Acad. Sci* ., 174 (1970) 5-10.
22. A. Verma, D. J. Hirsch, C. E. Glatt, G. V. Ronnett and S. H. Snyder, Carbon monoxide: a putative neural messanger, *Science* , 259 (1993) 381-384.
23. P. A. Rodgers, H. J. Vreman, P. A. Dennery and D. K. Stevenson, D. K., Sources of carbon monoxide (CO) in biological systems and applications of CO detection technologies, *Semin Perinatol* ,18 (1994) 2-10.
24. H. Yuyi, S. Qianwen, Y. Jin and J. Yong, Hydrogen sulfide: a gaseous signaling molecule modulates tissue homeostasis: implications in ophthalmic diseases, *Cell Death and Disease* (2019) 10 (2019) 293-304.
25. R. Wang, 2002. Two's company, three's a crowd: can H_2S be the third endogenous gaseous transmitter?,*FASEB J* ., 16 (2002) 1792-1798.
26. R. K. Olson, J. A. Donald, R. A. Dombkowski and S. F. Perry, Evolutionary and comparative aspects of nitric oxide, carbon monoxide and hydrogen sulfide, *Respir. Physiol. Neurobiol* ., 184 (2012) 117–129.
27. M. M. Gadalla and S. H. Snyder, Hydrogen sulfide as a gasotransmitter,*J. Neurochem* ., 113(2010) 14–26.
28. R. K. Olson, E. R. DeLeon and F. Liu, Controversies and conundrums in hydrogen sulfide biology, *Nitric Oxide* , 41, 11–26 (2014); B. Olas, Hydrogen sulfide in hemostasis: friend or foe?,*Chem.-Biol. Interact* ., 217(2014) 49.
29. R. K. Olson, Is hydrogen sulfide a circulating "gasotransmitter" in vertebrate blood?,*Biochim. Et. Biophys. ActaBioenerg* ., 1787 (2009) 856–863.
30. P. J. Hogg, Contribution of allosteric disulfide bonds to regulation of hemostasis, *J. Thromb. Haemost* ., 7 (2009) 13–16.
31. M. R. Mir, N. Jain, P. S. Jaget, W. Khan, P. K. Vishwakarma, D. K. Rajak, B. A. Malik and R. C. Maurya, Urinary tract anti-infectious potential of DFT-experimental composite analyzed ruthenium nitrosyl complex of N-dehydroaceticacid-thiosemicarbazide, *Journal of King Saud University-Science* ,31 (2019) 89–100.
32. J. M. Mir, N. Jain, P. S. Jaget and R. C. Maurya. Density Functionalized [Ru^{II}(NO)(Salen)(Cl)] Complex: computational,photodynamics and in vitro anticancer facets,*Photodiagnosis and Photodynamic Therapy* , 19 (2017) 363-374.
33. J. M. Mir, N. Jain, B. A. Malik, R. Chourasia, P. K. Vishwakarma. Urinary tract infection fighting potential of newly synthesized ruthenium carbonyl complex of N-dehydroacetic acid-N'-o-vanillin-ethylenediamine, *Inorg. Chim. Acta* , 467(2017) 80-92.
34. J. M. Mir, R. C. Maurya, A new Ru(II) carbonyl complex of 2-benzoylpyridine: Medicinal and material evaluation at the computational–experimental convergence. *J. Chin. Adv.. Mater. Soc.* , 6 (2018) 156-168.
35. J. M. Mir and R. C. Maurya, A gentle introduction to gasotransmitters with special reference to nitric oxide: Biological and chemical implications, *Rev. Inorg. Chem* .,38 (2018) 193–220.
36. J. M. Mir, B. A. Malik, M. W. Khan and R. C. Maurya, Molybdenum dinitrosyl Schiff base complexes of dehydroacetic acid and thiourea derivatives: DFT-experimental characterization and nosocomial anti-infectious implications, J. Chin. Chem. Soc., (2019)1–9; DOI:10.1002/jccs.201800337.
37. J. M. Mir and R. C. Maurya, Experimental and theoretical insights of a novel molybdenum(0) nicotine complex containing CN and NO as co-ligands, *J. Chin. Adv.. Mater. Soc.* , 2018;doi.org/10.1080/22243682.2018.1534608.
38. J. M. Mir, R. C. Maurya. Nitric oxide functionalized molybdenum (0) pyrazolone Schiff base complexes: thermal and biochemical study, RSC Adv., 8(2018) 35102–35130.
39. J. M. Mir and R. C. Maurya, Physiological and pathophysiological implications of hydrogen sulfide: A persuasion to change the fate of the dangerous molecule, *J. Chinese Adv. Mater.Soc* ., 2018; DOI:10.1080/22243682.2018.1493951.
40. R. C. Maurya and J. M. Mir, A Gentle Introduction to Gasotransmitters, NO, CO and H_2S, Lap

Posted on Authorea 23 Nov 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.160614188.83707688/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

Lambert Academic Publishing, Deutschland, Germany, ISBN: 978-3-330-01114-4 (2016) 1-309; R. C. Mauryaand J. M. Mir, "NO-, CO-, and H_2S-Based Metallopharmaceuticals", in "Advances in Metallodrugs: Preparation and Applications in Medical Chemistry", Shahid-ul-Islam, AtharAdilHashmi and Salman Ahmad Khan (Eds.), Scrivener Publishing LLC, Beverly, MA,ISBN: 978-1-119-64042-4(2020)157–202.A.

41. A. K. Mustafa, M. M. Gadallaand S. H. Snyder. Signaling by gasotransmitters, *Sci. Signal* , 2 (2009) 1-8. doi:10.1126/scisignal.268re2.
42. L. Li, P. Roseand P. K. Moore, Hydrogen sulfide and cell signaling,*Annu. Rev. Pharmacol. Toxicol* , 51(2011) 169–187.
43. R. F. Furchgott and J. V. Zawadzki, The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine,*Nature* , 288 (1980) 373–376.
44. A. Hermann, G. F. Sitdikova, T. M. Weiger (Eds.), Gasotransmitters: Physiology and Pathophysiology, Springer-Verlag (2012).
45. M. A. Marletta, Nitric oxide synthase structure and mechanism, J. Biol. Chem., 268(1993) 12231-12234; C. F. Nathan, Nitric oxide as a secretory product of mammalian cells, FASEB J 6(1992) 3051-3064.
46. U. Forstermannand H. Kleinert, Nitric oxide synthase: Expression and expressional control of the three isoforms, *Naunyn-Schmiedeberg's. Arch. Pharmacol* ., 352 (1995) 351-364;R. G. Knowles, S. Moncada, Nitric oxide synthases in mammals, *Biochem. J* ., 298 (1994) 249-258.
47. F. Becquet, Y. Courtois, O. Goureau,Nitric oxide decreases in vitro phagocytosis of photoreceptor outer segments by bovine retinal pigmented epithelial cells, *J. Cell. Physiol* . 159(1994) 259-262.
48. F. Becquet, Y. Courtois, and O. Goureau, Nitric Oxide in the eye: Multifaceted roles and diverse outcomes, *Surv. Ophthalmol* , 42 (1997) 71-82.
49. J. F. Kerwin, J. R. Lancaster and P. L. Feldman, Nitric oxide: a new paradigm for second messengers, *J. Med. Chem* ., 38 (1995) 4343-4362.
50. D. S. Bredt and S. H. Snyder, Nitric oxide: a physiologic messenger molecule, *Ann. Rev. Biochem* ., 63(1994) 175-195; J. Koistinaho, S. M. Sagar, NADPH diaphorase reactive neurones in the retina,*Prog. Ret. Eye Res* ., 15(1995) 69-87.
51. C. M. Venturini, R. G. Knowles, R. M. J. Palmer and S. Moncada, Synthesis of nitric oxide in the bovine retina,*Biochem. Biophys* . *Res. Comm* ., 180 (1991) 920-925.
52. O. Goureau, J. Bellot, B. Thillaye, Y. Courtois and Y. de Kozak, Increased nitric oxide production in endotoxin-induced uveitis: reduction of uveitis by an inhibitor of nitric oxide synthase. *J. Immunol* ., 154 (1995) 6518-6523.
53. A. Yoshida, N. Pozdnyakov, L. Dang and S. M. Orselli, Nitric oxide synthesis in retinal photoreceptor cells,*Visual Neuroscience* , 12(1995) 493-500.
54. N. N. Osborne. N. L. Barnett, A. J. Herrera, NADPH diaphorase localization and nitric oxide synthetase activity in the retina and anterior uvea of the rabbit eye, *Brain Res* ., 610 (1993) 194-198.
55. R. Yamamoto, D. S. Bredt, S. H. Snyder and R. A. Stone, The localization of nitric oxide synthase in the eye and related cranial ganglia, *Neurosci* ., 54 (1993)189-200.
56. K. Koch, H. Lambrecht, M. Haberecht, D. Redburn and H. H. Schmidt, Functional coupling of a Ca^{2+}/calmodulin dependent nitric oxide synthase and a soluble guanyl cyclase in vertebrate photoreceptor cells, EMBO J, 13(1994) 3312-3320.
57. M. T. R. Perez, B. Larsson, P. Aim, Localization of neuronal nitric oxide synthase-immunoreactivity in rat and rabbit retinas, Brain Res., 104(1995) 207-217.
58. B. A. Lieppe, C. Stone, J. Koistinaho, D. R. Copenhagen, Nitric oxide synthase in Muller cells and neurons of salamander and fish retina,*J. Neurosci* ., 14 (1994) 7641-7654.
59. J. T. Rosenbaum, H. O. MacDevitt, R. B. Guss, P. R. Egbert, Endotoxin-induced uveitis in rats as a model for human disease,*Nature* , 286 (1980) 611-613.
60. N. N. Osborne, N. L. Barnett, A. J. Herrera, NADPH diaphorase localization and nitric oxide synthetase activity in the retina and anterior uvea of the rabbit eye, *Brain Res* ., 610 (1993)194-198.
61. U. Chakravarthy, A. W. Stitt, J. McNally,J. R. Bailie, E. M. Hoeyand P Duprex, Nitric oxide synthase

Posted on Authorea 23 Nov 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.160614188.83707688/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

activity and expression in retinal capillary endothelial cells and pericytes, *Curr. Eye Res* ., 14 (1995) 285-294.

62. J. A. Nathanson, and McKee, Identification of an extensive system of nitric oxide-producing cells in the ciliary muscle and outflow pathway of the human eye, *Invest . Ophthalmol . Vis .Sci.* , 36 (1995)1765-1773.
63. O. Goureau, D. Hicks, Y. Courtois and Y. de Kozak, Induction and regulation of nitric oxide synthase in retinal Muller glial cells,*J. Neurochem* ., 63(1994)310-317.
64. O. Goureau, M. Lepoivre and Y. Courtois, Lipopolysaccharide andcytokines induce a macrophage-type of nitric oxide synthasein bovine retinal pigmented epithelial cells.*Biochem. Biophys. Res. Comm* ., 186 (1992) 854-859.
65. O. Goureau, D. Hicks and Y. Courtois, Human retinal pigmented epithelial cells produce nitric oxide in response to cytokines,*Biochem. Biophys. Res. Comm* ., 198 (1994) 120-126.
66. J. Liversidge, P. Grabowski, S. Ralston, Rat retinal pigment epithelial cells express an inducible form of nitric oxide synthase and produce nitric oxide in response to inflammatory cytokines and activated T cells, *Immunology* , 83 (1994) 404-409; J. R. Sparrow, C. F. Nathan, Y. Vodovotz, Cytokine regulation of nitric oxide synthase in mouse retinal pigment epithelial cells in culture,*Exp. Eye Res* ., 59(1004)129-139.
67. C. L. Hartsfield, Cross talk between carbon monoxide and nitric oxide,*Antioxid. Redox Signal* , 4 (2002) 301–307.
68. M. A. Gonzales and P. K. Mascharak, Photoactive metal carbonyl complexes as potential agents for targeted CO delivery, *J. Inorg . Biochem* ., 133 (2014) 127–135; T. R. Johnson, B. E. Mann, J. E. Clark, R. F., Colin J. Green and R. Motterlini, Metal carbonyls: a new class of pharmaceuticals ?, *Angew. Chem. Int. Ed.* , 42 (2003) 3722-3729.
69. M. D. Maine, The heme oxygenase system: A regulator of second messenger gases, *Annu. Rev. Pharmacol . Toxicol.* , 37(1997) 517-554.
70. R. Tenhunen, H. S. Marver and R. Schmid, Microsomal heme oxygenase: Characterization of the enzyme, *J. Biol. Chem* ., 1969, 244, 6388-6394.
71. R. Schmid, A. F. McDonagh, ThePorphyrins, Vol. VI (Ed.: D. Dolphin), Academic Press, New York (1979) 257-293.
72. R. Motterlini, A. Gonzales, R. Foresti, J. E. Clark, C. J. Green and R. M. Winslow, Heme oxygenase-1-derived carbon monoxide contributes to the suppression of acute hypertensive responses in vivo,*Circ.Res.* , 83(1998) 568-577.
73. T. R. Johnson, B. E. Mann, J. E. Clark, R. F., Colin J. Green and R. Motterlini, Metal carbonyls: a new class of pharmaceuticals ?,*Angew. Chem. Int. Ed.* , 42(2003) 3722-3729.
74. L. J. Ignarro, G. Cirino, A. Alessandro and C. Napoli,Nitric oxide as a signalling molecule in the vascular system: an overview, *J. Cardiovasc. Pharmacol* ., 34 (1999) 879-886.
75. L. J. Ignarro, Nitric Oxide: Biology and Pathobiology, Academic Press, San Diego, 2000.
76. D. M. Lawson, C. E. M. Stevenson, C. R. Andrew and R. E. Eady, Unprecedented proximal binding of nitric oxide to heme: implications for guanylate cyclase, *EMBO J* ., 19 (2000) 5661-5671.
77. J. R. Stone and M. A. Marletta, Soluble guanylate cyclase from bovine lung: activation with nitric oxide and carbon monoxide and spectral characterization of the ferrous and ferric states,*Biochemistry* , 33(1994) 5636-5640.
78. G. Deinum, J. R. Stone, G. T. Babcock and M. A. Marletta, Binding of nitric oxide and carbon monoxide to soluble guanylate cyclase as observed with Resonance Raman Spectroscopy, *Biochemistry* , 1996, 35, 1540-1547.
79. E. Martin, K. Czarnecki, V. Jayaraman, F. Murad and J. Kincaid,Resonance Raman and Infrared Spectroscopic Studies of High-Output Forms of Human Soluble Guanylyl Cyclase, *J. Am. Chem. Soc* ., 127 (2005) 4625-4631.
80. M. A. Gonzales and P. K. Mascharak, Photoactive metal carbonyl complexes as potential agents for targeted CO delivery, *J. Inorg. Biochem.* , 133 (2014) 127–135.
81. S. Ghatta, D. Nimmagadda, X. Xu and S.T. O'Rourke, Large-conductance, calcium-activated potas-

Posted on Authorea 23 Nov 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.160614188.83707688/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

sium channels: structural and functional implications,*Pharmacol. Therapeut* ., 110 (2006)103-116.
82. W. Zhao, J. Zhang, Y. Lu and R. Wang, The vasorelaxant effect of H_2S as a novel endogenous gaseous K_{ATP}channel opener, EMBO J, 20 (2001) 6008–6016.
83. L. Li, P. Rose and P. K. Moore, Hydrogen sulfide and cell signaling,*Ann. Rev. Pharmacol . Toxicol* ., 51(2011) 169–187.
84. R. Wang, Physiological implications of hydrogen sulfide: a whiff exploration that blossomed, *Physiol. Rev* ., 92 (2012) 791–896.
85. M. Ishigami, K. Hiraki, K. Umemura, Y. Ogasawara, K. Ishii and H. Kimura, A source of hydrogen sulfide and a mechanism of its release in the brain, *Antioxidants& Redox Signaling* , 11(2009) 205–214.
86. N. Shibuya, M. Tanaka, M. Yoshida, Y. Ogasawara, T. Togawa, K. Ishii and H. Kimura,3-Mercaptopyruvate sulfurtransferase produces hydrogen sulfide and bound sulfanesulfur in the brain, Antioxidants & Redox Signaling 11(2009) 703–714.
87. Y. Mikami, N. Shibuya, Y. Kimura, N. Nagahara, Y. Ogasawara and H. Kimura, Thioredoxin and dihydrolipoic acid are required for 3-mercaptopyruvate sulfurtransferaseto produce hydrogen sulphide,*Biochemical Journal* , 439(2011) 479–485.
88. C. Persa, K. Osmotherly, C. W. Chen, S. Moon, and M. F. Louabcd, The distribution of cystathionine β-synthase (CBS) in the eye: Implication of the presence of a trans-sulfuration pathway for oxidative stress defense, *Exp. Eye Res* . 83(2006) 817–823
89. W. W Pong, R. Stouracova, N. Frank, J. P. Kraus and W. D. Eldred, Comparative localization of cystathionineβ-synthase and cystathionineγ-lyase in retina: differences between amphibians and mammals, *J. Comp. Neurol* ., 505 (2010) 158–165.
90. Y. Mikami, N. Shibuya, Yuka Kimura, N. Nagahara, M. Yamada and H. Kimura, Hydrogen sulfide protects the retina from light-induced degeneration by the modulation of Ca^{2+}influx,*J. Biol. Chem* ., 286 (2011) 39379-39386.
91. N. Shibuya, S. Koike, M. Tanaka, M. Ishigami-Yuasa, Y. Kimura, Y. Ogasawara, K. Fukui, N. Nagahara and H. Kimura, A novel pathway for the production of hydrogen sulfide from D-cysteine in mammalian cells, *Nat. Commun* , 4 (2013)1-7;DOI: 10.1038/ncomms2371
92. M. Kulkarni, Y. F. Njie-Mbye, I. Okpobiri, M. Zhao, C. A. Opere, S. E. Ohia, Endogenous production of hydrogen sulfide in isolated bovine eye, *Neurochem. Res* ., 36(2011) 1540–1545.
93. J. D. Picker and H. L. Levy, Homocystinuria caused by cystathionine beta-synthase deficiency, University of Washington, Seattle (2010).
94. M. Yu, G. Sturgill-Short, P. Ganapathy, A. Tawfik, N. S. Peachey, and S. B. Smith, Age-related changes in visual function in cystathionine-beta- synthase mutant mice, a model of hyperhomocysteinemia, *Exp. Eye Res* ., 96 (2012)124–131.
95. P. S. Ganapathy, B. Moister, P. Roon, B. A. Mysona, J. Duplantier, Y. Dun, T. K. V. E. Moister, M. J. Farley, P. D. Prasad, K. Liu and S. B. Smith, Endogenous elevation of homocysteine induces retinal neuron death in the cystathionine-β-synthase mutant mouse, *Invest. Ophthalmol .Vis. Sci* ., 50 (2009) 4460–4470.
96. A. Tawfik, S. Markand , M. Al-Shabrawey, J. N. Mayo, J. Reynolds, S. E. Bearden, V. Ganapathy and S. B. Smith, Alterations of retinal vasculature in cystathionine-β-synthase heterozygous mice: a model of mild to moderate hyperhomocysteinemia, *Am. J. Pathol* ., 184 (2014) 2573–2585.
97. C. Bayse, ACS Symposium Series, American Chemical Society, Washington DC, 2013.
98. M. N. Hughes, N. M. Centellesand K. P. Moore, Making and working with hydrogen sulfide: the chemistry and generation of hydrogen sulfide*in vitro* and its measurement *in vivo* : a review,*Free Radic. Biol. Med* ., 47(2009)1346–1353.
99. M. C. Belardinelli, A. Chabli, B. Chadefaux-Vekemans and P. Kamoun, Urinary sulphur compounds in Down syndrome, *Clin. Chem.,* 47 (2001) 1500–1501.
100. K. Fischer, J. Chen, M. Petri and J. Gmehling, Solubility of H_2S and CO_2 in N-octyl-2-pyrrolidone and of H_2S in methanol and benzene, *AIChE J* , 48(2002)887–893.
101. E. A. Guenther, K. S. Johnson and K. H. Coale, Direct ultraviolet spectrophotometric determination of total sulfide and iodide in natural waters, Anal. Chem., 73 (2001)3481–3487.

Posted on Authorea 23 Nov 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.160614188.83707688/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

102. R. O. Beauchamp Jr., J. S. Bus, J. A. Popp, C. J. Boreiko and D. A. Andjelkovich, A critical review of the literature on hydrogen sulfide toxicity, *Crit. Rev. Toxicol* , 1964, 13,25–97.
103. R. J. Reiffenstein, W. C. Hulbert, S. H. Roth. Toxicology of hydrogen sulphide, *Annu. Rev. Pharmacol. Toxicol* , 32 (1992) 109–134.
104. S. Kage, S. Kashimura, H. Ikeda, K. Kudo and N. Ikeda, Fatal and nonfatal poisoning by hydrogen sulfide at an industrial waste site,*J. Forensic Sci* , 47 (2002) 652–655.
105. G. C. Y. Chiou, Review: Effects of Nitric Oxide on Eye Diseases and Their Treatment, *J. Ocul. Pharmacol. Ther* ., 17 (2001)189-198.
106. M. Goldstein, P. Ostwald and S. Roth, Nitric Oxide: A Review of Its Role in Retinal Function and Disease, *Vision Res* ., 36 (1996) 2979-2994.
107. A.Yadav, R. Choudhary and S. H. Bodakhe, Role of Nitric Oxide in the Development of Cataract Formation in $CdCl_2$-induced Hypertensive Animals, *Current Eye Research* . 43 (2018) 1454-1464.
108. R. Balasubramanian, A. Bui, X. Dong, L. Gan, Lhx9 is required for the development of retinal nitric oxide-synthesizing amacrine cell subtype,*Mol.Neurobiol* ., 55 (2018) 2922–2933.
109. Y. C. Tham, X. Li, T. Y. Wong, H. A. Quigley, T. Aung and C. Y. Cheng CY, Global prevalence of glaucoma and projections of glaucoma burden through 2040: A systematic review and meta-analysis,*Ophthalmology* , 121 (2014) 2081-90.
110. H. A. Quigley and A. T. Broman, The number of people with glaucoma worldwide in 2010 and 2020, *Br. J. Ophthalmol* ., 90 (2006) 262-267.
111. L. K. Wareham, E. S. Buys and R. M. Sappington, The Nitric Oxide-Guanylate Cyclase Pathway and Glaucoma, *Nitric Oxide* , 77(2018) 75–87.
112. M. S. Son, C. H. Park and J. W. Kim, Effect of Valproic Acid on Nitric Oxide and Nitric Oxide Synthase in Trabecular Meshwork Cell, *J. Korean Ophthalmol. Soc* ., 9 (2018) 543-548.
113. M. E. Cavet , H. H. DeCory,The Role of nitric oxide in the intraocular pressure lowering efficacy of latanoprostenebunod: Review of nonclinical studies, *J. Ocul. Pharmacol. Ther* .,34 (2017) 52-60.
114. J. M. Mir and R. C. Maurya, NO news is good news for eyes: A mini review, *Ann. Ophthalmol. Vis. Sci* ., 1(2018) 1003.
115. J. A. Nathanson, Nitrovasodilators as a new class of ocular hypotensive agents, *J. Pharmacol* . *Exp. Ther* ., 260 (1992) 956-965.
116. H. Kotikoski, P. Alajuuma, E. Moilanen, P. Salmenperä, O. Oksala, P. Laippala and H. Vapaatalo, Comparison of nitric oxide donors in lowering intraocular pressure in rabbits: Role of cyclic GMP, *J. Ocul. Pharmacol. Ther* ., 18 (2002)11-23.
117. F. F. Behar-Cohen, O. Goureau, F. D'Hermies F, Y. Courtois and Y. Courtois, Decreased intraocular pressure induced by nitric oxide donors is correlated to nitrite production in the rabbit eye,*Invest. Ophthalmol* . *Vis. Sci* ., 37(1996)1711-1715.
118. T. Sugiyama, T. Kida, K. Mizuno, S. Kojima and T. Ikeda, Involvement of nitric oxide in the ocular hypotensive action of nipradilol,*Curr. Eye Res* ., 23(2001)346-351.
119. M. Orihashi, Y. Shima, H. Tsuneki and I. Kimura, Potent reduction of intraocular pressure by nipradilol plus latanoprost in ocular hypertensive rabbits, *Biol. Pharm. Bull* ., 28 (2005) 65-68.
120. J.Y. Hu, B. Katz, Non-arteritic ischemic optic neuropathy and supplemental nitric oxide usage,*Am. J. Ophthalmol. Case Rep.,* 11 (2018) 26–27.
121. A. Mahmud, M. Hennessy and J. Feely, Effect of sildenafil on blood pressure and arterial wave reflection in treated hypertensive men.*J. Hum. Hypertens* ., 15 (2001)707-713.
122. S. S. Hayreh, Erectile Dysfunction Drugs and Non-Arteritic Anterior Ischemic Optic Neuropathy: Is There a Cause and Effect Relationship?,*J. Neuro-Ophthalmol* ., 25(2005) 295–298.
123. S. S. Hayreh, P. A. Podhajsky and B. Zimmerman, Non-arteritic anterior ischemic optic neuropathy: time of onset of visual loss, *Am. J. Ophthalmol* .,124(1997) 641-647.
124. M. E. Cavet and H. H. DeCory, The Role of Nitric Oxide in the Intraocular Pressure Lowering Efficacy of LatanoprosteneBunod: Review of Nonclinical Studies, *J. Ocul. Pharma. and Therap* ., 34 (2018) 52-60.
125. F. Galassi, E. Masini, B. Giambene, F. Fabrizi, C. Uliva, M. Bolla and E Ongini, A topical nitric

Posted on Authorea 23 Nov 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.160614188.83707688/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

oxide-releasing dexamethasone derivative: effects on intraocular pressure and ocular haemodynamics in a rabbit glaucoma model, *Br. J. Ophthalmol.* , 90 (2006) 1414-1419.

126. F. Impagnatiello, E. Bastia1, N. Almirante, S. Brambilla, B. Duquesroix, A. C. Kothe and M. V. W. Bergamini,Prostaglandin analogues and nitric oxide contribution in the treatment of ocular hypertension and glaucoma, *British Journal of Pharmacology* , 176 (2019)1079–1089; L. K. Wareham, E. S. Buys and R. M. Sappington, The Nitric Oxide-Guanylate Cyclase Pathway and Glaucoma, *Nitric Oxide,*77(2018) 75-87;Q. Huang, E. Y. Rui, M. Cobbs, D. M. Dinh, H. J. Gukasyan, J. A. Lafontaine, S. Mehta, B. D. Patterson, D. A. Rewolinski, P. F. Richardson and M. P. Edwards, Design, synthesis, and evaluation of NO-donor containing carbonic anhydrase inhibitors to lower intraocular pressure, J. Med. Chem., 58 (2015) 2821–2833
127. D. Sambhara and A. A. Aref, Glaucoma management: relative value and place in therapy of available drug treatments, *Ther. Adv.Chronic Dis* ., 5(2014)30–43.
128. J. Harding, *Cataract, Biochemistry, Epidemiology and Pharmacology* , Chapman & Hall, New York (1991).
129. J. A. Bawer, B. P. Booth, and H. L. Fung, *Nitric oxide donors: Biochemical pharmacology and therapeutics* , In*Nitric Oxide, Biochemistry, Molecular Biology and Therapeutic Implications* , Editors, L. Ignarro, and F. Murad, Academic Press, New York, pp. 361–381 (1995).
130. R. Gaudana, H. K. Ananthula, A. Parenky and A. K. Mitra, Ocular Drug Delivery, *The AAPS Journal* , 12 (2010) 348-360.
131. C. Bucolo and F. Drago, Carbon monoxide and the eye: Implications for glaucoma therapy,Pharmacology& Therapeutics 130 (2011) 191–201.
132. V. H. Lee and J. R. Robinson,Topical Ocular Drug Delivery: Recent Developments and Future Challenges, *J. Ocul. Pharmacol* ., 2 (1986) 67-108.
133. S. Macha, A. K. Mitra, and P. M. Hughes, Overview of ocular drug delivery, In A. K.Mitra (Ed.), Ophthalmic drug delivery systems (pp. 1-12), New York: MarcelDekker, Inc. (2003).
134. A. Sommer, J. M. Tielsch, J. Katz, H. A. Quigley, J. D. Gottsch, J. Javitt and K. Singh, Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans: the Baltimore eye survey,*Archives of Ophthalmology* , 109 (1991)1090-1095.
135. E. Stagni, M. G. Privitera, C. Bucolo, G. M. Leggio, R. Motterlini, and F. Drago, A water-soluble carbon monoxide-releasing molecule (CORM-3) lowers intraocular pressure in rabbits, *British Journal of Ophthalmology* , 93 (2009) 254-257.
136. X. Gasull, E. Ferrer, A. Llobet, A. Castellano, J. M. Nicolas, J. Pales, and A. Gual, Cell membrane stretch modulates the high-conductance Ca^{2+}-activated K^{+}channel in bovine trabecular meshwork cells, *Invest. Ophthalmol. Vis. Sci.,* 44 (2003)706-714.
137. D. Wakefield, J. H. Chang, Epidemiology of uveitis, *Int. Ophthalmol. Clin* . 45 (2005) 1–13.
138. P. Fagone, K. Mangano, S. Mammana, E. Cavalli, R. D. Marco, M. L. Barcellona, L. Salvatorelli, G. Magro, F. Nicoletti, Carbon monoxide-releasing molecule-A1 (CORM-A1) improves clinical signs of experimental autoimmune uveoretinitis (EAU) in rats, *Clinical Immunology* ,157(2015) 198–204
139. C. Szabo, Hydrogen sulphide and its therapeutic potential, Nat. Rev. Drug Discov., 6 (2007) 917–935.
140. F. Maggio, Glaucomas, *Top. Companion Anim. Med* . 30 (2015) 86–96.
141. A. V. Mantravadi and N. Vadhar, Glaucoma, *Prim. Care Clin. Off. Pract* ., 42 (2015)

437–449.

1. H. Neufeld, D. K. Dueker, T. Vegge and M. L. Sears, Adenosine 3', 5'-monophosphateincreases the outflow of aqueous humour from the rabbit eye, *Invest. Ophthalmol* ., 14 (1975) 40-42.
2. J. Robinson, E. Okoro, C. Ezuedu , L. Bush , C. A. Opere, S. E. Ohia, Y. F. Njie-Mbye, Effects of hydrogen sulfide-releasing compounds on aqueous humor outflow facility in porcine ocular anterior segments, ex vivo, *J. Ocul. Pharmacol* ., 33(2017) 91-97.
3. K. Modis, P. Panopoulos,G. Olah,C. ColettaA. Papapetropoulos and C. Szabo, Role of phosphodiesterase inhibition and modulation of mitochondrial cAMP levels in the bioenergetic effect of hydrogen sulfide in isolated mitochondria. Nitric oxide, 31(2013) S28.

Posted on Authorea 23 Nov 2020 — The copyright holder is the author/funder. All rights reserved. No reuse without permission. — https://doi.org/10.22541/au.160614188.83707688/v1 — This a preprint and has not been peer reviewed. Data may be preliminary.

4. E. Perrino, C. Uliva, C. Lanzi, P. D. Soldato, E. Masini and A. Sparatore, New prostaglandin derivative for glaucoma treatment,*Bioorg. Med. Chem. Lett* ., 19 (2009)1639–1642.
5. A. Salvi, P. Bankhele, J. Jamil, M. KulkarniChitnis, Y. F. Njie-Mbye, S. E. Ohia and C. A. Opere, Effect of hydrogen sulfide donors on intraocular pressure in rabbits. *J. OcularPharmacol. Therapeut* ., 32 (2016) 371–375.