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Review Article

Biochemical Tale of CO in the Vale of Eye: a Mini Review

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Abstract:

Carbon monoxide (CO) is one of the biologically significant members of “gasotransmitters” known to have multiple roles in maintaining mammalian homeostasis. This molecule at non-optimal level is toxic for mammalian physiology. Like nitric oxide, this gaseous molecule found associated with metabolic pathways of heme-oxygenase, has profound implications on maintaining healthy eyesight. CO donors or CO-releasing molecules have also sound applications in normalizing Intra Ocular Pressure (IOP). Therefore, the CO is related with the ophthalmic control. In addition to rectify optical defects the antimicrobial efficiency of CO and its releasers represent fascinating area of research. Hence, the related compounds are supposed to act as a shield for both the infectious as well as the non-infectious eye defects.

Keywords: gasotransmitters; ophthalmic diseases; CO; CORMs

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. Carbon monoxide (CO) has long been known as a dangerous gas for mammals and is called as a “silent killer” [3]. Carbon monoxide, when inhaled enters the bloodstream, formscarboxyhaemoglobin (COHb) at a rate 240 times greater than oxygen [4]. This reduces the oxygen transport ability and results in hypoxia [5]. Biologically, CO is considered as a by-product of heme oxygenase (HO) metabolism [6], and in the early stage of its biological exploration, CO was found as a chronic neurotransmitting agent [7]. Therefore, the further studies have altered the general perception of CO as a harmful molecule [8]. 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. 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 towards pharmaceutical aspects of NO, CO and H_2S –based systems [9-17], and also, due to profound bio-actions of CO-tagged compounds on eye, herein a mini review in connection with CO-role in eye is reported. A historical view of the emergence of the term "gasotransmitter", within the production of CO in mammals, and to seek strong sponsors of CORMS (in the event of chronic biosynthesis and digestion) applicable in the most common eye-defects are the main objectives of this literature update.

2.Concept of “Gasotransmitters”:

In general, gasotransmitters refer to the distinctive class of molecules like NO, CO and H_2S, responsible for communication amongst body cells for a particular biological action. Albeit, these molecules exist in solvated form while in biological medium, the respective differences 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 [18]. The properties and functional diversity found in these bioessential signalling molecules, therefore gave rise to coin a new term in reference to their biological relevance as “gasotransmitters”.

2.1. 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 [19,20]. 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 [21]. The metabolic pathwayof HO-catalyzed haem oxidation involves several important stages as has been illustrated in Figure 1. In addition to CO other intermediatory products like of a-meso-hydroxyheme, verdoheme, biliverdin (converts to bilirubin as excretory product conjugated by glucoronic acid shown in Figure 2) are also involved. [22,23]. The bioaction of HO-1 under stressful situation gets enhanced and the CO-production gets increased than the optimal value [24]. 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 [25]. Hence, the detection level of CO because of inducible HO-1 can help in diagnosis of pathophysiological state.

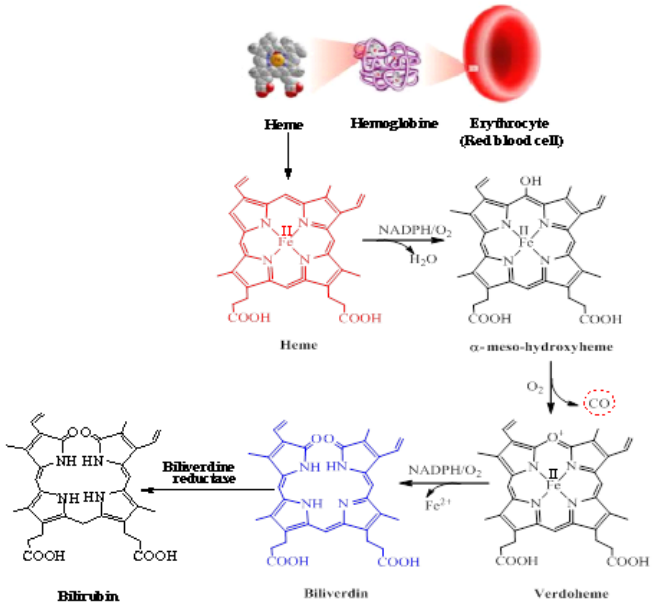


Figure 1: Oxidation of heme by heme oxygenase (HO) forming CO as a by-product.

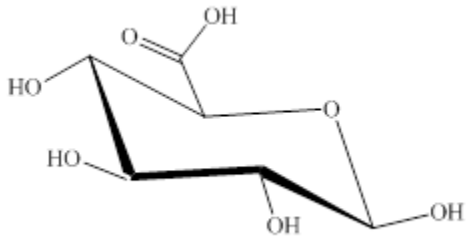


Figure 2: Chemical structure of Glucuronic acid

3.CO 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 CO in maintaining a healthy eye, so is the title established as “the aim of CO gasotransmitter in the mission of vision”.

1. Carbon monoxide, CORMS and the ocular system:

Glaucoma as discussed earlier is an optic neuropathy and is considered as the major cause of eye defects in advanced countries [26-32]. 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) and filtering surgery of galucoma. As the main threat for glaucoma is elevated IOP, hence is the first target to be corrected in the treatment plan [33]. 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 [26]. CORM-3 as shown in Figure 3 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 [34].The 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.

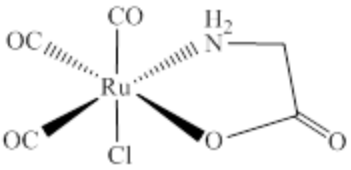


Figure 3: Chemical structure of CORM-3

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 4**, linking the pathways, TM with Schlemm's canal. It is expected that CO exhibits this action byreducing the volume of TM cell [35].

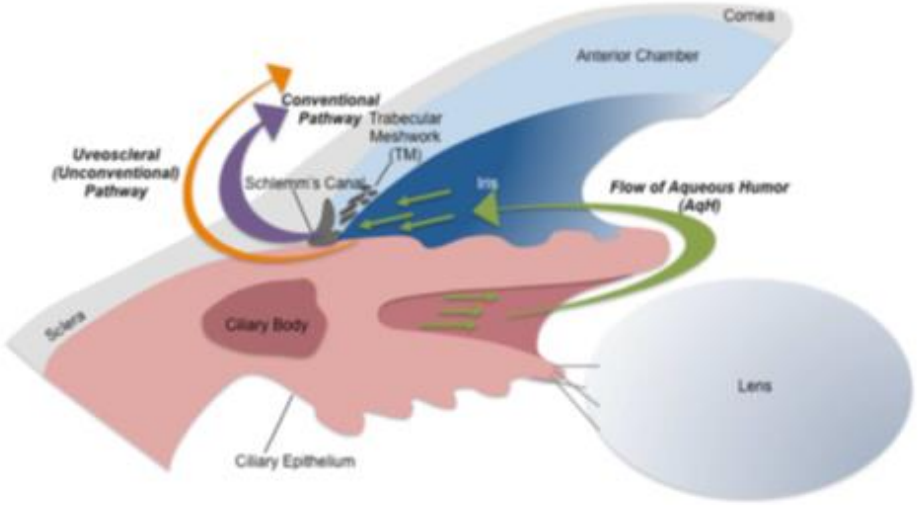


Figure 4: Diagram displaying the production and flow of aqueous humour (AqH).

The yearly rate of incidence of uveitis (a sight-threatening inflammatory disease of the eye) at the age between 20 and 60 years for both males and females is estimated to be with a frequency of 38–714 per 1,00,000 persons [36]. 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 5 and Scheme 1 may be referred for knowing the structural details and CO-releasing process. Nicoletti et al. [37] showed that CORM-A1is helpful in autoimmune responsive in uveoretinitis.

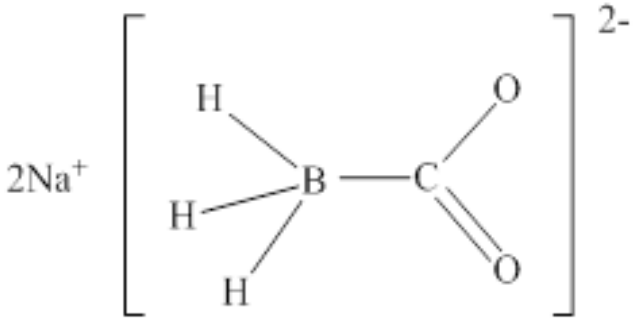
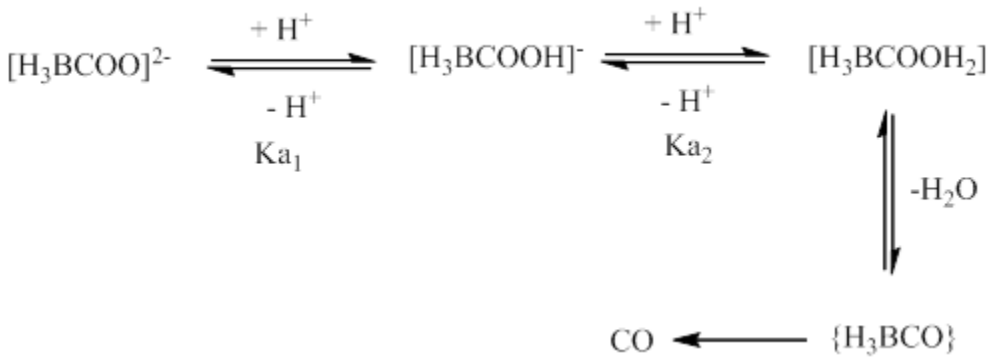


Figure 5: Chemical structure of CORM-A1



Scheme 1: Mechanism of CO release fromCORM-A1

4.Concluding Remarks and Future Outlook:

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 clinically 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 CO. 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 'CORMs?

Disclosures:

Authors do not have any conflict of interest to declare.

Ethical Statement:

All the data presented herein is original and extracted from literature sources under ethical rules and suitable citations have been made wherever necessary.

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