

Protecting the aging eye with hydrogen sulfide¹

Akash K. George, Rubens P. Homme, Dragana Stanisic, Suresh C. Tyagi, and Mahavir Singh

Abstract: Research demonstrates that senescence is associated with tissue and organ dysfunction, and the eye is no exception. Sequelae arising from aging have been well defined as distinct clinical entities and vision impairment has significant psychosocial consequences. Retina and adjacent tissues like retinal pigmented epithelium and choroid are the key structures that are required for visual perception. Any structural and functional changes in retinal layers and blood retinal barrier could lead to age-related macular degeneration, diabetic retinopathy, and glaucoma. Further, there are significant oxygen gradients in the eye that can lead to excessive reactive oxygen species, resulting in endoplasmic reticulum and mitochondrial stress response. These radicals are source of functional and morphological impairment in retinal pigmented epithelium and retinal ganglion cells. Therefore, ocular diseases could be summarized as disturbance in the redox homeostasis. Hyperhomocysteinemia is a risk factor and causes vascular occlusive disease of the retina. Interestingly, hydrogen sulfide (H₂S) has been proven to be an effective antioxidant agent, and it can help treat diseases by alleviating stress and inflammation. Concurrent glutamate excitotoxicity, endoplasmic reticulum stress, and microglia activation are also linked to stress; thus, H₂S may offer additional interventional strategy. A refined understanding of the aging eye along with H₂S biology and pharmacology may help guide newer therapies for the eye.

Key words: hyperhomocysteinemia, inflammation, redox homeostasis, senescence, vision impairment.

Résumé : Les recherches montrent que la sénescence est associée à des dysfonctionnements tissulaires et organiques et que l'œil ne fait pas exception à la règle. Les séquelles découlant du vieillissement ont été bien caractérisées comme étant des entités cliniques distinctes et les troubles de la vue ont des conséquences psychosociales importantes. La rétine et les tissus adjacents comme l'épithélium rétinien pigmenté (ERP) et la choroïde constituent des structures clés qui sont nécessaires pour la perception visuelle. Toute modification structurelle ou fonctionnelle des couches rétinienne et des barrières hémorétiniennes (BHR) peuvent mener à la dégénérescence maculaire liée à l'âge (DMLA), à la rétinopathie diabétique (RD) et au glaucome. En outre, il existe dans l'œil des gradients d'oxygène importants, qui peuvent mener à un excès de dérivés réactifs de l'oxygène (DRO) entraînant une réaction de stress dans le réticulum endoplasmique (RE) et les mitochondries. Ces radicaux sont à la base de troubles fonctionnels et morphologiques dans l'ERP et les cellules ganglionnaires rétinienne (CGR). Par conséquent, les maladies oculaires pourraient se résumer à des perturbations de l'homéostasie du système redox. L'hyperhomocystéinémie (HHcy) constitue un facteur de risque et entraîne une maladie vasculaire occlusive de la rétine. Il est intéressant de noter que le sulfure d'hydrogène (H₂S) s'est révélé être un agent antioxydant efficace, et qu'il peut contribuer au traitement de maladies en entraînant une atténuation du stress et de l'inflammation. En concomitance, l'excitotoxicité du glutamate, le stress du RE et l'activation de la microglie sont aussi liés au stress, et le H₂S pourrait donc permettre d'obtenir des stratégies interventionnelles supplémentaires. Une compréhension affinée du vieillissement de l'œil, ainsi que de la biologie et de la pharmacologie du H₂S pourrait contribuer à guider de nouveaux traitements pour les yeux. [Traduit par la Rédaction]

Mots-clés : hyperhomocystéinémie, inflammation, homéostasie du système redox, sénescence, trouble de la vue.

Introduction

Advances in medicine and technology have contributed to a marked increase in average life expectancy during the past few decades. As a result, age-related health issues are rising and thus causing a great burden on the healthcare system (Newgard and Sharpless 2013). Nonetheless, the aging process is often accompanied by numerous instances of age-associated dysfunction, which affects a broad range of cells, tissues, organs, and systems including the eye. Retina in the eye and its adjacent supporting tissues like retinal pigmented epithelium (RPE) and choroid are critical

structures that are essentially required for normal visual perception. Similarly, the blood retinal barrier (BRB) has three components: (1) inner blood-retina barrier, formed by tight junctions between retinal vascular endothelial cells; (2) outer blood-retina barrier, formed by tight junctions between RPE cells; and (3) blood aqueous barrier that is formed by tight junctions in the non-pigmented epithelial layer of the ciliary body, and the endothelium of the iris vasculature. A functional BRB is maintained by the neurovascular unit (Metea and Newman 2007), which composed of vascular endothelial cells, pericytes, glial cells, and

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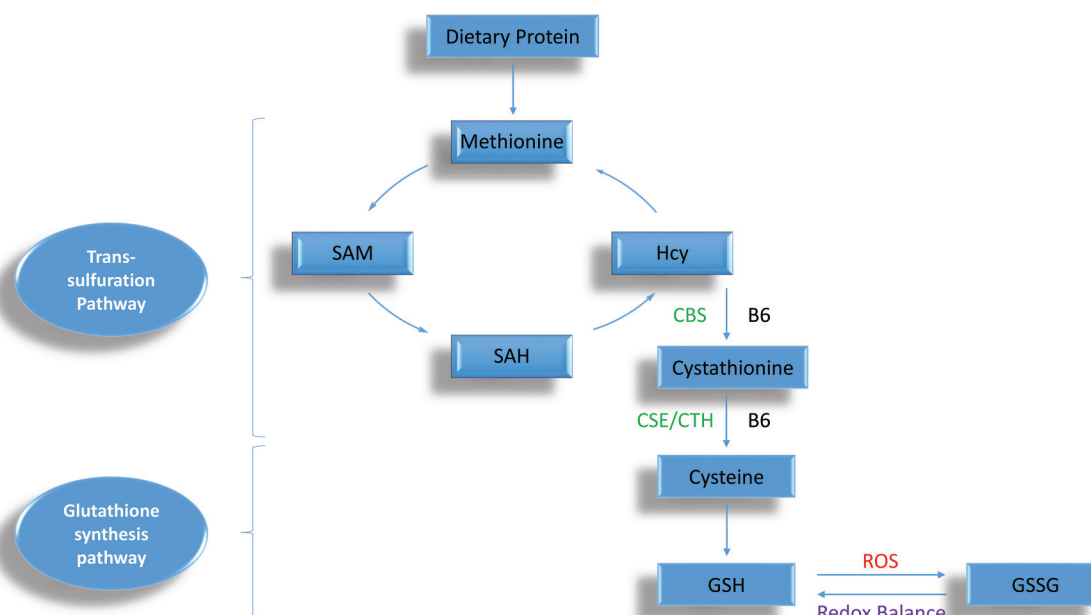
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Fig. 1. Homocysteine (Hcy) metabolism and glutathione (GSH) synthesis. The trans-sulfuration pathway converts methionine to cysteine, which is then converted to GSH. CBS, cystathionine- β synthase; CSE/CTH, cystathionine γ -lyase or cystathionase; GSSG, glutathione disulfide; ROS, reactive oxygen species; SAH, S-adenosyl homocysteine; SAM, S-adenosyl methionine. [Color online.]



neurons (Muio et al. 2014). Because the retina is composed of many layers, an unusual change in these layers has been implicated in common retinal associated diseases contributing significantly to vision loss or even blindness, and it is linked with age, and increases markedly with the aging process (Congdon et al. 2003, 2004; Pascolini and Mariotti 2012; Friedman et al. 2004a, 2004b). The cause for their association with aging are not well understood, but nonetheless these diseases are characterized by vascular dysfunction, neuronal apoptosis, and retinal neuroinflammation that may promote disease progression (Wax and Tezel 2009; Buschini et al. 2011). It is worth mentioning here that hyperhomocysteinemia (HHcy), a metabolic disorder that frequently occurs in the elderly population as reported in several reports, has further suggested that abnormalities in homocysteine (Hcy) metabolism implicating HHcy as a metabolic link in the multi-factorial process is part and parcel in many geriatric illness including retinal associated diseases (Ventura et al. 2001a, 2001b). The retinal diseases, and their irreversible damage to vision, and refractory characteristics as a result of neurodegeneration make them a hot area for ophthalmologists all over the world in association with oxidative stress that is also involved in several eye diseases (Barot et al. 2011; Williams 2008; George et al. 2019a; Novikova et al. 2014). Aging, gene abnormalities, and other stressors are very much like HHcy that increase oxidative stress, and subsequently the endoplasmic reticulum (ER) stress thus imposing cellular/tissue/organ/systemic level dysfunction (Biswas 2016; Reuter et al. 2010; Gill et al. 2010; Tsubota 2007). Here, we discuss the role of hydrogen sulfide (H_2S) in alleviating ocular dysfunction, especially during aging, and their better management. Retinal degenerative diseases including glaucoma, age-related macular degeneration (AMD), and diabetic retinopathy (DR) share pathological basis of abnormal structure and functional characteristics of retinal neurons that result in an irreversible damage to visual acuity (Cottet and Schorderet 2009). The respective H_2S levels and expression of cystathionine- β synthase (CBS), cystathionine- γ lyase (CSE), and 3-mercaptopyruvate sulfur transferase (3-MST) in the retinal tissues were found to be significantly decreased along with the loss of retinal ganglion cells. Similarly, oxidative stress

plays an important and pivotal role in the development and progression of multiple neurodegenerative disorders, including amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, and Huntington's disease (Niedzielska et al. 2016). H_2S performs multiple crucial roles in physiology and pathophysiology of various systems in the body, such as the nervous, cardiovascular, gastrointestinal, and respiratory systems. Abe and Kimura discovered H_2S as an important gasotransmitter (Abe and Kimura 1996). Since then, H_2S has been found to be involved physiologically and pathologically in neuroregulation (Perez et al. 2014), vasodilatation (Hosoki et al. 1997), endocrinologic regulation (Kaneko et al. 2006), and inflammation (Du et al. 2014). The role of endogenous H_2S and its physiological effect in the retina is still being researched; however, strong evidence shows that endogenous H_2S plays numerous protective roles in physiological aspects of the eye and its vision. The mechanisms for its effect on inhibiting ischemic injury, reducing oxidative stress damage, regulating apoptosis, and reducing inflammation are being worked out. Nowadays, H_2S is noticed as an endogenously produced signaling molecule with various pathophysiological effects. H_2S seems to be involved in several ocular diseases including pathologies related to aging. In this review, we highlight some of the effects and actions of H_2S in several age-related pathologies of retinal associated diseases along with treatment with H_2S that has shown to mitigate conditions by suppressing oxidative stress levels, as well as reducing inflammation (Fig. 1).

HHcy

Hcy has been studied extensively for over 30 years for its unique involvement in an increasing number of human diseases. The sulfur-containing amino acid Hcy is an intermediate product derived from methionine metabolism (methionine cycle). Although normally the synthesis and elimination of Hcy are in balance, but in disease condition i.e., in HHcy, plasma Hcy levels increase significantly. There are mainly four ways people can develop HHcy: (1) excessive consumption of methionine-rich protein diet; (2) vitamin B_{12} /folate deficiency; (3) heterozygous/homozygous CBS enzyme activity; and (4) obstruction of Hcy renal clearance. Several other factors such as age, sex, physical activity, alcohol intake, smoking, and a host

of co-morbidities can modulate methionine cycle and increase the relative Hcy levels in blood (Diakoumopoulou et al. 2005). Elevated plasma Hcy concentration, or in other words HHcy, may induce excessive production of reactive oxygen species (ROS) and impair the glutathione-related antioxidant defense system thus leading to greater oxidative stress and lower antioxidant enzymatic activities (Huang et al. 2001; Starkebaum and Harlan 1986; Menegola et al. 1996; Nishio and Watanabe 1997). In every metabolic process, certain amounts of pro-oxidative ROS are formed. Intracellular milieu is predominantly a reducing environment firstly, due to the presence of enzyme activities like glutathione peroxidase, superoxide dismutase, and catalase, which break down ROS into water and oxygen and secondly a series of redox defense systems can inactivate ROS, which are reduced glutathione (GSH), nicotinamide adenine dinucleotide hydrogen (NADH), thioredoxin, and free radical scavengers (Yamamoto et al. 2003; Zima et al. 2004; Gasparetto et al. 2005). However, when there is an imbalance between free radical production and antioxidant capacity, that triggers oxidative stress generation (Rainbolt et al. 2014). Thiols can auto-oxidize leading to the formation of ROS. Hcy has already been shown to demonstrate association in glutamate excitotoxicity (Ho et al. 2002). In fact, many studies showed that Hcy induced a pro-oxidant action through hydrogen peroxide production during metal-catalyzed oxidation and, in the presence of nitric oxide, the superoxide anion can form powerful oxidant peroxynitrite (Loscalzo 1996). Thus, indicating that oxidative stress plays a key role in the pathogenesis of retinal associated diseases was reported by our group recently (George et al. 2018). Mildly elevated plasma levels of total Hcy are associated with atherosclerosis, myocardial infarction, carotid artery stenosis, venous thrombosis, and stroke, suggesting a central role of Hcy in the pathogenesis of atherothrombotic disease (Selhub et al. 1995; Boushey et al. 1995; Graham et al. 1997; Stanger et al. 2001). High levels of Hcy in the blood as a risk factor for various vascular eye diseases have been observed and associated with several eye conditions (Weger et al. 2001, 2002a, 2002b, 2002c).

HHcy and AMD

AMD is a leading cause of blindness in developed countries, particularly in people older than 60 years (Ratnapriya and Chew 2013). AMD causes damage to the outer retina, choriocapillaris, RPE, and Bruch's membrane. The disease is characterized by structural changes within Bruch's membrane that then lead to cellular changes in the RPE including loss of RPE cells and the eventual development of advanced forms of the disorder. It is responsible for many visual impairments in the world and therefore newer approaches are urgently needed to develop effective treatment options to prevent blindness. Several risk factors have been postulated and, based upon them, treatments have been developed, namely photodynamic therapy, vascular endothelial growth factor, or vascular endothelial growth factor receptor inhibitors that are currently available to AMD patients but none of them leads to a permanent cure or prevention from the dreaded disease. Intravitreal injection of Hcy in normal wild-type mice resulted in diffuse hyper-fluorescence, albumin leakage, and choroidal neovascularization in RPE. In vitro experiments on ARPE-19 showed that Hcy dose dependently reduced tight junction protein expression, increased fluorescein isothiocyanate dextran leakage, decreased transcellular electrical resistance, and impaired phagocytic activities. Collectively, the results demonstrated detrimental effects of excess Hcy levels (HHcy) on RPE structure and functions that could lead to the development of AMD-disease-like features (Ibrahim et al. 2016). Also, there is increasing evidence that clearly supports a role for inflammation in a number of eye diseases including AMD and, as a result, some studies have suggested a risk association with plasma Hcy to be an independent factor for inflammation in the eye (Rutar et al. 2015; George et al. 2018; Singh and Tyagi 2017a, 2017b, 2017c, 2018). Hcy can also alter tissue properties through generations of ROS that can activate matrix metalloproteinases that

can be extruded into the matrix (Vacek et al. 2013). High levels of Hcy adversely affect the vascular endothelium and it is elevated in individuals who suffer from AMD (Axer-Siegel et al. 2004). Because Hcy levels >15 mmol/L are considered abnormal, we studied changes in retinal cells employing different concentrations of Hcy to evaluate effects on genes related with inflammatory cytokines and their receptors (George et al. 2018, 2019c, 2020; Homme et al. 2018; Singh et al. 2019; Singh and Tyagi 2017a, 2017b, 2017c, 2018). HHcy induced the changes in vasculature and the antioxidant status predisposed to AMD susceptibility because of the reduced blood supply to macula causing hypoxia and tissue malfunctioning (Sergejeva et al. 2016). Epidemiological studies and the systematic evaluations comparing plasma Hcy (Fig. 1) in AMD patients and control subjects also confirmed that results are consistent with an independent association between higher Hcy levels (HHcy) and AMD cases and that low vitamin B₁₂ levels were independently associated with an increased risk (Haas et al. 2011; Mulero et al. 2014; Qin et al. 2014; Tanaka et al. 2011; Seddon et al. 2006; Rochtchina et al. 2007; Huang et al. 2015; Keles et al. 2014).

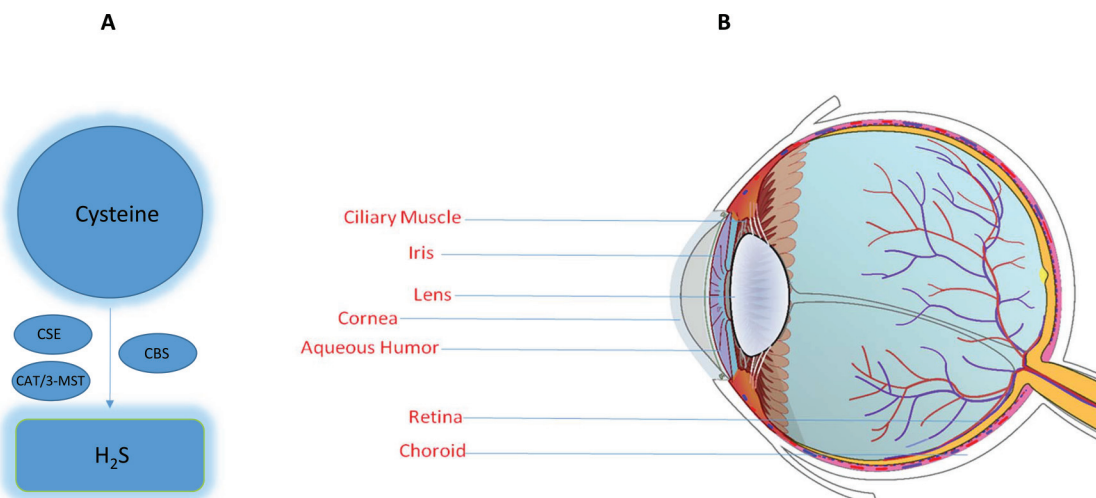
HHcy and DR

DR is a complication of diabetes mellitus (DM) and is a leading cause of reduced visual acuity and acquired blindness in the working-age adult population in both developed and developing nations (Congdon et al. 2003). Elevation of Hcy leads to vascular dysfunctions in patients, suggesting HHcy is one of the crucial risk factors (Aydin et al. 2008; Zarkin 2004; Ambati et al. 2003). Diabetic related abnormalities often lead to systemic inflammation via modulation of several inflammation-related genes, their respective gene products, Hcy metabolism, and pyroptosis (Homme et al. 2018). It should be emphasized that diabetes can affect almost all parts of our visual system because early clinical events of DR in patients and animals with DM include retinal glial dysfunction, neurodegeneration, and vascular dysfunction (Gori et al. 2005; Kern and Barber 2008; Ali and El-Remessy 2009). Although laser therapy has shown partial therapeutic effect on DR, the current treatments for DR are far from satisfactory. As the prevalence of DR progressively rises throughout the world, there is an urgent need for researching and developing more specific therapeutic strategies to alleviate patients' suffering. It has been reported that DM has positive relationships between DR and Hcy as mentioned previously (Chiarelli et al. 2000; Targher et al. 2000; Vaccaro et al. 2000; Agardh et al. 1994). Hcy may be related to prolonged diabetic duration and DR (Huang et al. 2006), also related to increased risk for proliferative retinopathy (Agullo-Ortuno et al. 2002; Bahadir et al. 2015; de Luis et al. 2005; Looker et al. 2003; Shukla et al. 2004; Smulders et al. 1999; Ukin et al. 2009; Wang et al. 2012; Aydin et al. 2008). A high prevalence of retinopathy was found in patients with type 2 DM who had fasting Hcy concentrations greater than 15 μ mol/L (Agullo-Ortuno et al. 2002; Hoogeveen et al. 2000). Inflammation plays an essential role in the early pathogenesis of DR. Later, as the disease progresses, a corresponding increase in inflammatory factors along with adhesion leukocyte to the inflamed endothelium affect the integrity of the BRB, resulting in the panoply of retinovascular diseases, including DR (Kern 2007).

HHcy and glaucoma

Glaucoma is a major healthcare-associated morbidity worldwide with an approximately 60 million people affected by glaucomatous optic neuropathy, while three-quarters of these cases are open-angle glaucoma (Cook and Foster 2012). It is more common in older adults and it is an irreversible blinding neurodegenerative disease that is characterized by progressive loss of retinal ganglion cells. The risk factors for developing glaucoma include race, age, family history, and elevated intraocular pressure (Kwon et al. 2009; Czudowska et al. 2010). Other risk factors include hypertension, DM, vitamin B₁₂ deficiency, and folic acid deficiency (Zhao

Fig. 2. (A) Generation of endogenous H_2S . (B) Multiple ocular cells/tissues showing the presence of endogenous H_2S . The highest concentrations of endogenous H_2S are detected in cornea and retina, of which the production differs in their major enzymes. 3-MST, 3-mercaptopyruvate sulfur transferase; CAT, cysteine aminotransferase; CBS, cystathionine- β synthase; CSE, cystathionine γ -lyase. [Color online.]



et al. 2014, 2015). Both elevated Hcy levels and glaucoma were found to be related to increased risk of vascular disease (Lonn et al. 2006; Fruchart et al. 2004; Jeganathan et al. 2009). HHcy induces changes in microvasculature of the optic nerve head and impairs optic nerve blood flow and ocular vasculopathy via a vasoconstrictive effect, smooth muscle proliferation, endothelial injury, thrombogenesis, platelet activation, and apoptotic cell death in retinal ganglion cells (Cattaneo 1999; Lipton et al. 1997; Hankey and Eikelboom 2001; Finkelstein 1998; Bleich et al. 2002; Roedel et al. 2007; Leibovitch et al. 2003; Wang et al. 2004; Cumurcu et al. 2006; Atalay et al. 2019; Schorah et al. 1998; Turgut et al. 2010; Xu et al. 2012).

HHcy and optic neuropathy

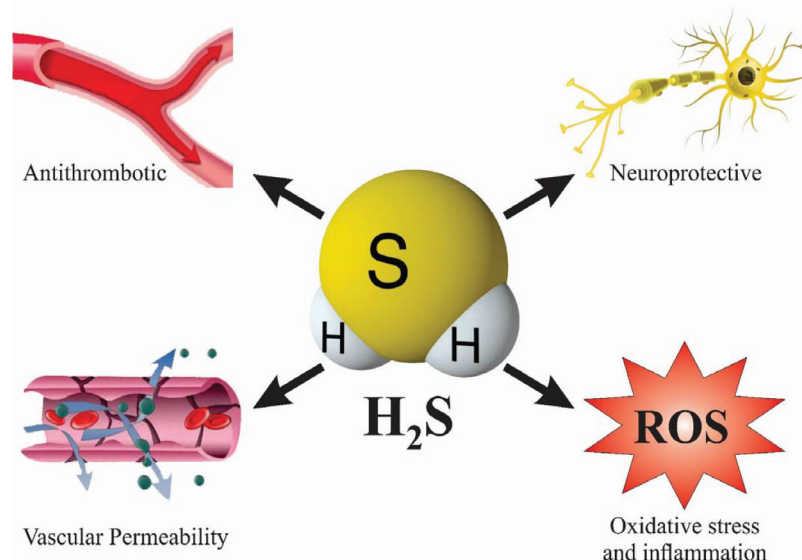
Non-arteritic ischemic optic neuropathy and retinal vascular occlusion are severe ocular pathologies and common causes of visual impairment. Patients older than 50 years of age are primarily affected and the visual deficits are frequently persistent. The underlying pathomechanisms may include endothelial damage, and dysfunction, arteriosclerotic alterations of the vessel wall with turbulent and (or) insufficient blood flow, intraluminal thrombus formation, and embolism. Consequently, arterial hypertension, DM, smoking, increased plasma lipoprotein(a) levels, and hyper viscosity have been identified as risk factors (Baumal and Brown 1997; Brown 1991a, Brown 1991b; Brown et al. 1990, 1993, 2002, Duker and Brown 1989; Vander et al. 1990; Talks et al. 1995; Wong et al. 2005). In brief, Hcy levels is highly linked with these conditions (Stanger et al. 2005).

HHcy, age-related retinal disorders, and their management by H_2S

Hcy is formed by demethylation of methionine and, as mentioned earlier, it is an emerging risk factor for DR and cardiovascular disease that has gradually elicited the interest of researchers worldwide (Chico et al. 1998). Increased Hcy level in blood or HHcy acts as a crucial trigger for oxidative stress that leads to the overproduction of ROS, associated with a failure in the antioxidant system causing cellular oxidative stress (Tyagi et al. 2005; Farinati et al. 2010; Alfadda and Sallam 2012; Rahal et al. 2014). Oxidative stress mediated inflammatory process in eyes of susceptible hosts that can lead to the beginning of subtle pathological changes triggers the degenerative and inflammatory cascade in the retina

(Singh and Tyagi 2017a, 2017b, 2017c). Age-related dysregulation of immune response in the retina can contribute to disease pathogenesis (Xu et al. 2009; Wong 2013). As microglia are the primary resident immune cells in the retina, and are long-lived ones that persist across long periods of chronological time, and the senescent changes occurring within aging microglia may be one cause of immune response “failure”, conferring upon the retina an age-dependent vulnerability to diseases (Albini et al. 2005; Ajami et al. 2007). Glutamate can also activate microglia and enhance cytokine-induced neurodegeneration (Minami et al. 1991). H_2S is an endogenous gasotransmitter with significant pathophysiological importance, but its role in retinal diseases is still under intense investigation. H_2S is produced endogenously in various parts of the body such as the central nervous system (CNS), heart, blood, and vascular smooth muscle cells (Zhao et al. 2001). H_2S is generated from L-cysteine by CBS, CSE, and (or) 3-MST (Fig. 2A). To date, four enzymatic pathways that regulate endogenous H_2S production have been revealed: CBS, CSE (Stipanuk and Beck 1982; Abe and Kimura 1996), CAT/3-MST (Shibuya et al. 2009a, 2009b; Tanizawa 2011), and D-amino acid oxidase/3MST (Shibuya et al. 2013). So far, only the first three endogenous H_2S synthesis pathways have been reported to be involved in the retinal tissue that detected the expression of endogenous H_2S producing enzymes in each layer of the retina in mice (Fig. 2B) (Pong et al. 2007; Mikami et al. 2011; Gersztenkorn et al. 2016; Kulkarni et al. 2011). In the CNS, H_2S regulate synaptic activities as a neurotransmitter (Kimura et al. 2005). Ion channels and transporters were found to be involved in the regulatory effects of H_2S on CNS (Tang et al. 2010; Kimura 2011b). A few studies of the physiologic effects of H_2S in the retina showing the presence of H_2S and its endogenous synthesis pathway in the retina as well as the fact that deficiency of CBS may lead to retinal degeneration and detachment indicate that H_2S plays an important role in the eye as a gaseous neuromodulator (Bublil et al. 2016; Majtan et al. 2018; Orendac et al. 2003). For example, by regulating Ca^{2+} influx, H_2S can protect retinal neurons against light-induced degeneration and it was found to have a prominent relaxation effect on the retina arteries by acting on the ion channel, indicating that H_2S may play an important role in regulating the retina vascular system (Takır et al. 2015). Disturbance in calcium transport system exists in retinal Muller cells as well as RPE may contribute to the retinal degenerative diseases (Bringmann et al. 2000; Wimmers et al. 2007). The counteraction intracellular Ca^{2+} and H_2S in the retina

Fig. 3. H₂S mitigates hyperhomocysteinemia (HHcy)-induced oxidative stress and inflammation. It also helps mitigate the blood retinal barrier permeability and exerts an antithrombotic coupled with neuroprotective effects. Further, it modulates the retinal blood flow. ROS, reactive oxygen species. [Color online.]



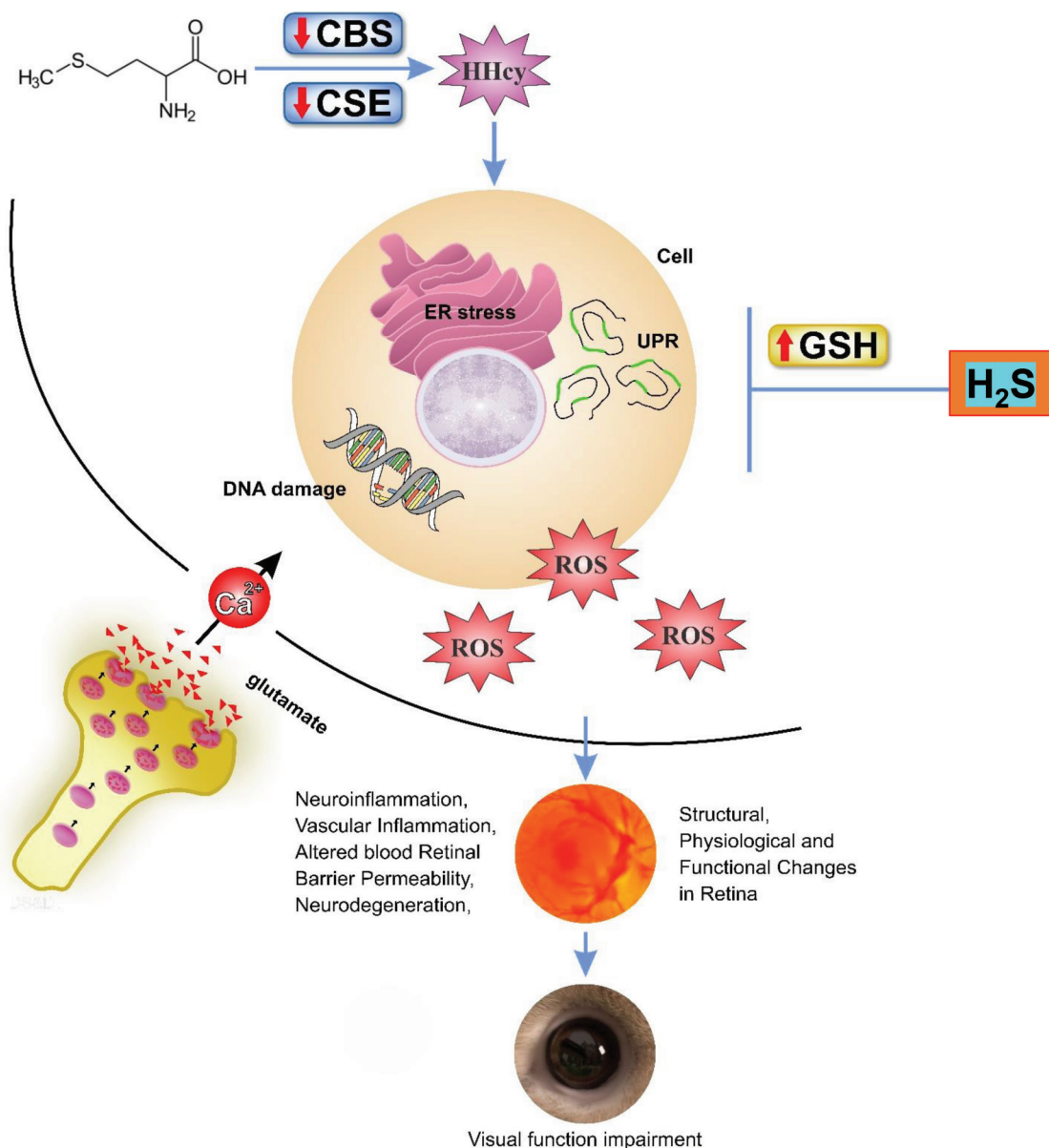
mediated the protective effect of H₂S on the retinal photoreceptor apoptosis caused by light-induced damage (Mikami et al. 2011). It is reported that sodium and chloride channels play crucial roles in various physiologic processes in the retina (Zhang et al. 2011; Smith et al. 2017). Therefore, further investigations need to be done to explore the possible relationship between retina-derived H₂S and the ion channels especially that play a key role in the fast-excitatory synaptic transmission in the CNS. Also, the glutamate aspartate transporter is located in retinal Muller cells and is involved in maintaining GSH balance with the toxic effects of glutamate (Martin et al. 2012). Genetic expression profiling of the entire retina have shown that retinal aging encompasses gene sets involved in the regulation of local inflammatory responses, particularly those involved with the innate immune system, suggesting that modulatory influences onto microglia, possibly from neighboring retinal cells such as Muller cells, may change with aging (Wang et al. 2011, 2014; Wang and Wong 2014; Chen et al. 2010). Therefore, glutamate aspartate transporter might be a target of H₂S to regulate neurotransmission in the retina by exploring the potential association between the oxidative stress and ion channels especially the glutamate and the role of H₂S in its modulation could be used to develop new treatments for retinal associated diseases. Retinal cell degeneration and inflammation caused by ROS and elevated intracellular concentrations of Ca²⁺ are not able to correct by the endogenous H₂S or that may fail by various factors and that triggers the structural, physiological, and functional changes in the retina. Even under such conditions, the administration of H₂S may have clinical benefit for alleviating the ER stress, maintaining vascular tone (George et al. 2018), and of correcting disturbed glutaminergic system and microglia activation, is anticipated to have therapeutic potential to manage age-related retinal diseases.

Conclusion

Age-related eye diseases are alarmingly high and are responsible for most visual impairment in the world. Therefore, newer approaches are needed to develop effective treatment options to prevent blindness. Several risk factors have been postulated and, based upon them, a few treatments were developed but none

of them led to a permanent cure or prevention. To make things worse, metabolic disorders including elevated Hcy level or HHcy-mediated oxidative stress and inflammation have been associated in the etiology of vascular complication (Tyagi et al. 2005; George et al. 2018, 2019a; Majumder et al. 2018a, 2019a, 2019b; Singh et al. 2018). H₂S is now being referred as a gasotransmitter that easily penetrates plasma membrane and induces a wide spectrum of signaling cascades in target cells. Some studies in cellular and animal models have suggested several mechanisms to explain the protection afforded by H₂S, which include anti-inflammatory, anti-apoptotic, vasodilation, and alleviation of oxidative stress and neuroprotection (Calvert et al. 2010; Yang et al. 2007; Tang et al. 2008) (Fig. 3). H₂S also increases production of intracellular GSH, a major intracellular antioxidant promoting neuronal protection and improving brain function (Kimura et al. 2005; Kimura 2011a; Kimura and Kimura 2004; Nagai et al. 2004). In the past, H₂S has been proved as a neuromodulator in the eye with important effect in various retinal diseases; however, the role of H₂S in diseases, especially in retinal associated diseases, still needs to be investigated and in-depth studies of the underlying mechanisms are required. As we know, unlike CNS or cardiovascular system, the unique characteristic of the retina is the direct connection to the vitreous body, which is a perfect match to gaseous treatment that has been widely used in research for many retinal diseases like macular membrane disorders. In this review, we discussed the role(s) of H₂S in alleviating metabolically induced oxidative stress and inflammation such as HHcy that also increases simultaneously the ER stress, and the glutamate system dysfunction and microglia activation in retinal associated disease (George et al. 2019a). Innovative and effective antioxidative stress strategies would have tremendous impact on the trigger and the disease progression. The ability to successfully modulate microglial aging phenotype has the promise of “rejuvenating” the immune environment of the retina in ways that may be protective against the progression of age-related ocular diseases. Therefore, H₂S has tremendous potential to alleviate the oxidative and endoplasmic stress levels along with the chronic inflammation as a therapeutic potential for the better management of aging eye diseases employing H₂S-centered therapies (Fig. 4). While therapeutic potential of H₂S through quelling oxidative stress and inflammation is obvious, however, there could be

Fig. 4. A cartoon depicting the role of H₂S in reducing the deleterious effects as caused by hyperhomocysteinemia (HHcy) mediated redox imbalance, and inflammation that result in structural, physiological, and functional changes in the ocular compartment. CBS, cystathionine-β synthase; CSE, cystathionine γ-lyase; ER, endothelium reticulum; GSH, glutathione; UPR, unfolded protein response. [Color online.]



potential side effects if the dosage of the H₂S donor compound is not properly standardized. The higher concentration of H₂S does exhibit a variety of deleterious/cytotoxic effects but the lower concentration rather exerts powerful beneficial effects (George et al. 2018, 2019b; Majumder et al. 2018b, 2019b; Szabo et al. 2014).

Conflict of interest

The authors declare that there is no conflict of interest associated with this work.

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