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# Research Progress on the Role of Hydrogen Sulfide in the Pathological Process of Diabetic Retinopathy

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**Abstract:** As a gaseous signaling molecule, hydrogen sulfide ($H_2S$) plays a role in regulating organ development and sustaining tissue homeostasis. However, overexposure to this compound can lead to harmful effects, triggering cell toxicity, orchestrating pathological mechanisms, and raising the likelihood of multiple disorders. However, when present in appropriate amounts, this gasotransmitter is known to exert beneficial effects on biological systems. Recent research has shed light on the multifaceted effects of hydrogen sulfide, highlighting its ability to counteract oxidative stress, reduce inflammatory responses, and protect retinal tissues from structural and functional impairment. The application of slow-releasing $H_2S$-providing substances has shown potential as a therapeutic approach for various illnesses, This piece of research summarizes the biological roles played by the metabolism of hydrogen sulfide and explores its potential in treating eye-related conditions.

**Keywords:** Hydrogen Sulfide ($H_2S$); Diabetic Retinopathy (DR); Oxidative Stress (OS); Inflammation; Homocysteine.

## 1. Introduction

Over the past five decades, the incidence of diabetes worldwide has experienced a consistent upward trend, reaching epidemic levels [1]. According to statistics, the global diabetes prevalence stood at 9.3% (affecting 463 million individuals) in 2019, with projections indicating it will climb to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 [2]. Characterized by persistent high blood sugar, diabetes mellitus (DM) inflicts harm on multiple organ systems, especially the visual organs, kidneys, heart, and vascular network, potentially worsening other physiological dysfunctions [3]. Among its complications, diabetic retinopathy (DR) ranks among the most prevalent and represents a primary contributor to blindness [4]. Scientific investigations have established a strong link between oxidative stress and inflammatory processes in the development of DR [5]. Hydrogen sulfide ($H_2S$) is now recognized as an endogenous signaling gas in mammals [6]. As the third member of the gas-signaling family, $H_2S$ exhibits diverse biological activities, including antioxidant and cytoprotective effects, as well as vasodilatory, anti-inflammatory, and anti-fibrotic actions [7]. Despite extensive research, the exact molecular mechanisms driving DR pathology are still not fully understood. This review compiles existing studies regarding the impact of hydrogen sulfide on the pathological development of diabetic retinopathy.

## 2. Biological Properties of Hydrogen Sulphide

However, recent research has shifted the perception of $H_2S$, no longer merely classified as a harmful gas or a metabolic waste product [8]; instead, it is now identified as the third key gaseous signaling molecule, alongside carbon monoxide (CO) and nitric oxide (NO) [9], with diverse biological activities such as reducing inflammatory responses, counteracting oxidative stress, inhibiting tumor growth, modulating ion channel functions, and safeguarding cardiovascular health [10]. A set of three enzymes are responsible for generating $H_2S$ within the body: cystathionine-γ-lyase (CSE/CTH), cystathionine-β-synthase (CBS), and 3-mercaptopyruvate thiotransferase (3-MST/MPST) [11]. Among these, the synthesis process begins with the formation of L-cystathionine through a β-substitution reaction where homocysteine and serine interact, a reaction that is facilitated by CBS. Subsequently, CSE then catalyses the elimination of α- and γ-cysteine from L-cystathionine to yield L-cysteine. Following this process, the enzyme CSE, along with CBS, facilitates the β-elimination reaction of L-cysteine, resulting in the formation of $H_2S$. Following this process, the enzyme CSE, along with CBS, facilitates the β-elimination reaction of L-cysteine, resulting in the formation of $H_2S$. Additionally, L-cysteine undergoes conversion via cysteine aminotransferase (CAT), where the amine group of the amino acid is transferred to α-ketoglutarate, resulting in the formation of 3-mercaptopropanoic acid (3-mercaptopyruvate, 3-MP). 3-MP is then converted into hydrogen sulfide ($H_2S$) through the action of 3-mercaptopyruvate sulfurtransferase (3-MST) [12,13]. Both cystathionine β-synthase (CBS) and cystathionine γ-lyase (CTH) are enzymes that depend on pyridoxal 5'-phosphate and are located in the cell cytoplasm. CBS, which is mainly located in the brain and central nervous system, and CTH, primarily active in the cardiovascular system, can also be identified in the kidney, liver, lymphocytes, placenta, and islets, in addition to their main expression areas. MPST, which is located within mitochondria, has been identified in the heart, kidneys, liver, and retina. Notably, all three enzymes responsible for generating $H_2S$ are present within cardiovascular cells [14]. $H_2S$ concentrations in human tissues vary depending on measurement methods and donor age [15]. In peripheral blood, concentrations range from 30 μM to 300 μM. Its physiological concentration in the brain is approximately three times higher than in serum [16]. The therapeutic and toxic effects of $H_2S$ are concentration-dependent. Exposure to $H_2S$ (>700 ppm) causes loss of consciousness (syncope), respiratory paralysis, and may result in death. Concentrations of 300–700 ppm cause fainting, and exposure exceeding 30 minutes may sometimes prove fatal. Inhaling several breaths

of air containing high concentrations (>200–300 ppm) and prolonged exposure exceeding one hour results in respiratory paralysis [15].

(1) $H_2S$ possesses antioxidant stress-resistant properties

The complex interplay between hydrogen sulphide ($H_2S$) and oxidative stress (OS) has garnered substantial attention in various fields including molecular biology, biochemistry, and medical research [17]. Oxidative stress arises from an imbalance where reactive oxygen species (ROS) are produced more readily than the body can neutralize them with its detoxification mechanisms, which poses critical risks to cellular activity, tissue health, and the development of many pathological conditions [18]. $H_2S$ possesses antioxidant properties, inducing glutathione production and activating the Nrf2 pathway, both of which contribute to regulating oxidative stress and maintaining cellular redox balance [19].

(2) Eliminate reactive oxygen species

In the transsulfur pathway, cysteine plays a vital role as an antioxidant by contributing to the synthesis of glutathione (GSH), the primary antioxidant. Glutathione is created as a thiol-containing molecule through two sequential enzymatic reactions: first, L-glutamate and L-cysteine are joined by glutamate-cysteine ligase to form γ-glutamyl-L-cysteine, and then L-glycine is added to this intermediate by glutathione synthase to complete the process. Hydrogen sulfide, along with cysteine and glutathione, are all capable of eliminating reactive oxygen species through the formation of disulfide bonds from their -SH groups [20].

(3) Protein modification

Hydrogen sulphide has the ability to alter a wide range of proteins, such as kelch-like ECH-associated protein 1 (Keap1), nuclear factor kappa-B (NF-κB), and HIF-1α. A crucial cellular mechanism for combating oxidative stress involves the Keap1/Nrf2 pathway, which is one of the primary antioxidant pathways. Hydrogen sulfide ($H_2S$) has been shown to influence nuclear factor erythroid 2-related factor 2 (Nrf2) through the process of sulfuration of Keap1, which in turn leads to the activation of Nrf2 [21]. Nrf2 is recognised as a key regulator of transcriptional activation for genes involved in antioxidant defence, antioxidant biosynthesis, and metabolic adaptation [22]. This activation of Nrf2 subsequently results in the increased production of key reactive oxygen species (ROS) scavengers, including glutathione and thioredoxin (Trx). Additionally, Keap1 is also involved in driving the transcription of various antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase [20].

Trx is a multifunctional protein comprising 105 amino acids with a molecular weight of 12 kDa. It exists in two forms: oxidised (Trx-$S_2$) and reduced (Trx-$(SH)_2$). Trx catalyses disulphide bond reduction and quenches reactive oxygen species (ROS) by coupling with Trx-dependent peroxidases or peroxiredoxins[23]. As a key component, Trx plays a crucial role in the body's primary defense system against oxidative stress. This protein features two cysteine residues that possess redox-active properties, acting as a protective shield for proteins against the unnecessary formation of intermolecular or intramolecular disulphide bonds caused by oxidizing agents. Studies have revealed that hydrogen sulfide ($H_2S$) achieves its antioxidant properties by adjusting the redox balance of thioredoxin (Trx). This adjustment works to block the signaling cascade involving Trx, apoptosis signal-regulating kinase 1 (ASK1), and p38 mitogen-activated protein kinase (p38 MAPK) [24]. Furthermore, $H_2S$ influences cellular redox signaling processes by directly causing S-sulfhydration of the nuclear factor erythroid 2-related factor 2 (Nrf2)-thioredoxin pathway [25]. Through these mechanisms, $H_2S$ contributes to cellular protection against oxidative stress-related damage [26].

(4) The anti-inflammatory capacity of $H_2S$

Inflammation is the body's biological reaction to tissue damage. However, when inflammation spirals out of control, it can trigger the development of various inflammatory disorders [27]. $H_2S$ plays a pertinent role in coordinating the recruitment and infiltration of immune cells into tissues, a process critical to the generation of inflammatory responses. $H_2S$ inhibits leukocyte migration, reduces neutrophil infiltration, and induces neutrophil apoptosis, thereby preventing parenchymal tissue damage and enhancing anti-inflammatory effects [6,28]. Additionally, research indicates that $H_2S$ can also counteract inflammation by suppressing the activity of the NLRP3 inflammasome [29]. Furthermore, it is well-documented that the nuclear factor kappa B (NF-κB) pathway is a key regulator of inflammatory signaling cascades, where its activation triggers the synthesis of pro-inflammatory cytokines like interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) after translocating into the cell nucleus. Recent studies have demonstrated that $H_2S$ can cause sulfhydration of the inhibitor of NF-κB (IκB), which in turn blocks NF-κB from translocating into the nucleus, thereby easing inflammatory responses [30,31].

# 3. The Association Between Hydrogen Sulphide and Diabetic Retinopathy

$H_2S$ is endogenously synthesised within ocular tissues. Carbonyl reductase beta (CBS) is distributed in both the retinal arterial endothelium and smooth muscle layer, whilst carbonyl reductase alpha (CSE) is primarily localised in the retinal arterial endothelium. Within the retina, CBS and CSE are expressed in cone-rod photoreceptor cells and retinal ganglion cells, with CSE also present in bipolar cells, though 3-methylthionine (3-MST) was found at the lowest levels [32]. Research indicates that treatment with $H_2S$ donors in diabetic retinopathy-induced mice alleviates retinal microvascular abnormalities, oxidative stress, and inflammation, whilst conferring neuronal protection [33].

(1) The Antioxidant and Anti-inflammatory Effects of $H_2S$ in Diabetic Retinopathy

ROS plays a pivotal role in the pathogenesis of diabetic retinopathy (DR), with its excessive accumulation damaging both the intravascular and perivascular tissues of the retina, ultimately leading to DR [34]. Importantly, mitochondria are not only major sources of ROS but also highly vulnerable to its harmful effects. Under persistent high blood glucose status, the electron transport chains within mitochondria become impaired, resulting in the generation of reactive oxygen species. This process further causes an elevation in proton leakage across the mitochondrial membrane and changes in mitochondrial membrane potential (MMP), which subsequently facilitates the release of cytochrome c, leading to the onset of apoptosis. This in turn sets off a harmful cycle involving a weakened capacity of antioxidant systems to neutralize free radicals, disruptions in the transcription and protein synthesis processes of mitochondrial DNA (mtDNA) that encodes mitochondrial proteins, and the impairment of DNA repair mechanisms, ultimately leading to mitochondrial dysfunction [35]. $H_2S$ can enhance GSH production by

increasing its redistribution to mitochondria via the cystathionine/cystathionine transporter, thereby protecting cells from oxidative stress. Moreover, $H_2S$ generation within mitochondria may directly suppress oxidative stress. Following ischaemia-reperfusion (I/R) injury, mitochondrial $H_2S$ exerts protective effects by inhibiting cytochrome oxidase activity, upregulating superoxide dismutase (SOD) levels, and downregulating reactive oxygen species (ROS) levels. Under hypoxic conditions, $H_2S$ further exerts neuroprotective effects by enhancing GSH synthesis, regulating CSE transport to mitochondria, and modulating ATP supply [36]. Studies indicate that NaHS (an $H_2S$ donor) treatment alleviates mitochondrial dysfunction in streptozotocin-induced diabetic rat models [37].

In rodent models of diabetic retinopathy, studies have revealed that high blood sugar levels lead to the accumulation of white blood cells in retinal blood vessels, a phenomenon that is linked to the programmed cell death of retinal cells and the blockage of capillary vessels. Hydrogen sulphide exerts anti-inflammatory actions by influencing macrophage phagocytic activity and enhancing granulocyte viability, processes that involve the suppression of p38 phosphorylation and the reduction of caspase-3 cleavage. Additionally, this compound can reduce myeloperoxidase (MPO) levels in neutrophilic cells, consequently lessening specific harmful impacts. Additionally, in diabetic retinopathy (DR) models, heightened retinal expression of intercellular adhesion molecule-1 (ICAM-1) and enhanced leukocyte adhesion to blood vessels have been documented, though $H_2S$ administration is reported to suppress ICAM-1 levels in vascular endothelial cells under high-glucose environments [38]. Studies indicate that $H_2S$ treatment of streptozotocin-induced diabetic rat retinas mitigates oxidative stress, alleviates mitochondrial dysfunction, inhibits NF-κB activation, and reduces inflammation [37].In diabetic retinopathy (DR), high-glucose-stimulated secretion of IL-18 and IL-1β by retinal pigment epithelial (RPE) cells is induced via NLRP3 activation and reactive oxygen species (ROS) production. Within human retinal pigment epithelial cells (ARPE-19), high glucose promotes cell death whilst also upregulating NLRP3 inflammasome expression and enhancing ROS generation. $H_2S$ protects human retinal pigment epithelium (HRPE) cells from serious glucose-induced damage by inhibiting ROS formation and NLRP3 inflammasome activation [11,39]. Consequently, $H_2S$ is considered to exert significant antioxidant and anti-inflammatory protective effects on retinal cells during the pathophysiology of DR.

(2) The Retinal Protective Effects of $H_2S$ in Diabetic Retinopathy

When the body is in a state of high blood sugar, glucose molecules will chemically combine with the amino groups at the ends of protein chains without the participation of enzymes, resulting in the gradual buildup of advanced glycation end products, which are known to play a crucial role in the progression of diabetic retinopathy. These accumulated AGEs can link up with various proteins inside cells, causing structural changes in these proteins and impairing their normal biological functions, which in turn disrupts important metabolic processes like the production of energy molecules such as ATP. AGEs, by impairing the electron transport chain (ETC), contribute to the escalation of oxidative stress, thereby enhancing the generation of reactive oxygen species (ROS). In addition, the increased ROS levels can accelerate the synthesis of more AGEs, leading to a self-reinforcing cycle that exacerbates the problem. AGEs undermine the integrity of the blood-retinal barrier (BRB), leading to oxidative stress and inflammation [34,35]. Hydrogen sulphide ($H_2S$) enhances galactose metabolism to reduce neuronal AGE production and suppress excessive oxidative stress [38]. In diabetic retinopathy (DR), NaHS treatment reduces BRB permeability and acellular capillary formation while decreasing VEGF levels and its signalling pathways in the vitreous, suggesting that retinal-derived $H_2S$ may protect against hyperglycaemia-induced retinal microvascular pathology [48]. Previous studies show that $H_2S$ has neuroprotective properties when exposed to both internal and external neurotoxins. Specifically, neuroprotective actions can be achieved by S-sulfhydration of critical regulatory factors involved in antioxidant mechanisms (Sirt1, Nrf2) and inflammatory processes (NF-κB), which in turn regulate downstream signaling cascades such as SIRT1/TORC1/CREB/BDNF-TrkB, Nrf2/ARE/HO-1, and other related pathways. Conversely, $H_2S$ appears to exert direct detoxification effects by binding endogenous and exogenous neurotoxins, thereby mitigating their toxicity [19]. The neuroprotective effects of $H_2S$ may relate to its inhibition of glial cell activation, oxidative phosphorylation, pro-inflammatory pathways, and inflammatory responses, alongside its reduction of oxidative stress and downregulation of retinal autophagy. Exogenous $H_2S$ donors have demonstrated potential in protecting retinal ganglion cells (RGCs) from diabetic retinopathy (DR) and ischaemia/reperfusion (I/R) injury [36]. The retinal protective effects of $H_2S$ donors may offer a novel therapeutic strategy to inhibit the progression of diabetic retinopathy.

(3) Hydrogen sulphide plays a dual role in diabetic retinopathy

In diabetic individuals, research has demonstrated the presence of heightened homocysteine concentrations. Homocysteine, a non-proteinogenic sulphur-containing amino acid, is now recognised as an independent risk factor for diabetic retinopathy [40]. $H_2S$ is a product of the homocysteine transsulfuration pathway [41]. Studies indicate that retinal homocysteine levels in donors with diabetic retinopathy are approximately threefold higher, while $H_2S$ levels are about 50% lower, compared to age-matched non-diabetic human control donors [42]. Under physiological conditions, homocysteine and $H_2S$ exhibit reciprocal regulation. Yet, a disturbance in the balance of homocysteine and $H_2S$ leads to heightened oxidative stress, heightened inflammatory responses, impaired mitochondrial function, and a decrease in the intracellular antioxidant GSH [42,43]. Investigations have revealed that the slow-release $H_2S$ donor GYY4137 not only halts the decline in $H_2S$ levels but also retards the progression of histopathological changes associated with diabetic retinopathy. In DR mice, GYY4137 administration has been shown to suppress retinal vascular leakage and functional deficits, while its intravitreal delivery mechanism protects ganglion cells from acute ischaemic injury and optic nerve compression, improving perfusion by dilating retinal vessels. In diabetic retinopathy (DR) mice, intravitreal administration has been shown to protect ganglion cells against acute ischaemic damage and optic nerve compression, while also enhancing retinal vessel dilation to improve blood perfusion. Additionally, GYY4137 halts the sequence involving oxidative stress leading to matrix metalloproteinase-9 (MMP-9) activation, which in turn increases mitochondrial damage, thus safeguarding

endothelial cells against faster cell death. This underlying protective pathway helps in hindering or slowing down the advancement of diabetic retinopathy[44].

When diabetes first develops, $H_2S$ serves as a safeguard against oxidative or nitrosative stress in the retina and vitreous humour. Additionally, when blood sugar levels are high, $H_2S$ is also believed to play a role in safeguarding the blood–retinal barrier (BRB) [38,45]. But as proliferative diabetic retinopathy (PDR) advances, higher homocysteine levels in PDR patients supply the raw material for $H_2S$ generation, resulting in higher concentrations of $H_2S$ in both the vitreous fluid and blood plasma. $H_2S$ could enhance the actions of vascular endothelial growth factor (VEGF) on vascular endothelial cells and the process of angiogenesis. In contrast, research focusing on $H_2S$ levels in the vitreous humor and blood plasma of patients with proliferative diabetic retinopathy (PDR) reveals that under high glucose conditions, the enzyme 3-MST loses its ability to catalyze the conversion of 3-MP to $H_2S$ within cells, consequently reducing its capacity to promote angiogenesis and cell growth. However, the proangiogenic effect of exogenous $H_2S$ is not diminished by hyperglycaemia. Additionally, the activity of $H_2S$-producing enzymes and the levels of this gas signal have been found to contribute to the development of retinal new blood vessels in situations where the eye's tissues are lacking oxygen. These observations imply that $H_2S$ could worsen retinal haemorrhage in advanced proliferative diabetic retinopathy [38,46,47]. $H_2S$ exhibits distinct roles in the pathophysiology of NPDR and PDR, indicating a dual function.

# 4. Summary and Outlook

Diabetic retinopathy (DR) is a globally significant retinal disease of increasing importance. It is also recognised as a substantial socioeconomic burden worldwide. The purpose of this review is to enhance understanding of hydrogen sulphide's dual role in DR progression and its potential as a therapeutic target. This review elucidates the cascade of metabolic abnormalities triggered by hyperglycaemia, including oxidative stress, inflammation, elevated homocysteine levels, and advanced glycation end-product (AGE) formation. These factors progressively induce mitochondrial dysfunction, compromise the blood-retinal barrier (BRB), and cause structural and functional retinal damage, thereby perpetuating a vicious cycle. Sustained-release therapy with $H_2S$ donors may represent a promising avenue for further investigation into DR, offering potential therapeutic targets. However, cellular experiments and animal model studies require additional information and insights to delineate $H_2S$'s dual role in DR for clinical trials. Consequently, further exploration of $H_2S$'s efficacy in treating DR, alongside the development of safe, effective, and well-tolerated $H_2S$ formulations for human use, could positively influence the appropriate management of this condition.

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