Recent Advances in the Role of Hydrogen Sulfide in Ischemia-Reperfusion Injury

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Abstract

When histiocyte are ischemic for a certain time and blood supply is suddenly restored, the pathological condition of rapidly aggravated tissue damage is called ischemia reperfusion injury, which is mainly caused by a large amount of Ca2+ influx and oxygen free radicals attacking ischemic histiocyte. Ischemia reperfusion injury can increase the incidence rate and mortality of some diseases, such as acute myocardial infarction, ischemic stroke, acute renal injury, intestinal obstruction, hyperkalemia and multiple organ failure, and it also brings great challenges to surgery such as organ transplantation. However, the current treatment methods for ischemia-reperfusion are still very limited. Fortunately, increasing evidence suggests that reasonable concentrations of hydrogen sulfide may play a powerful organ protective role in ischemia-reperfusion injury, mainly through mechanisms such as anti apoptotic, antioxidant, stress reduction, regulation of autophagy, and inhibition of inflammation. Therefore, hydrogen sulfide has profound clinical conversion prospects in the treatment of I/R injury. This article systematically summarizes the generation and physiological effects of endogenous hydrogen sulfide, as well as its protective mechanisms in different systems such as the heart, brain, kidney, liver, retina, and testes. In addition, the clinical transformation prospects and current challenges of hydrogen sulfide in ischemia-reperfusion injury were discussed.

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Abstract

When histiocyte are ischemic for a certain time and blood supply is suddenly restored, the pathological condition of rapidly aggravated tissue damage is called ischemia reperfusion injury, which is mainly caused

by a large amount of Ca^{2+} influx and oxygen free radicals attacking ischemic histiocyte. Ischemia reperfusion injury can increase the incidence rate and mortality of some diseases, such as acute myocardial infarction, ischemic stroke, acute renal injury, intestinal obstruction, hyperkalemia and multiple organ failure, and it also brings great challenges to surgery such as organ transplantation. However, the current treatment methods for ischemia-reperfusion are still very limited. Fortunately, increasing evidence suggests that reasonable concentrations of hydrogen sulfide may play a powerful organ protective role in ischemia-reperfusion injury, mainly through mechanisms such as anti apoptotic, antioxidant, stress reduction, regulation of autophagy, and inhibition of inflammation. Therefore, hydrogen sulfide has profound clinical conversion prospects in the treatment of I/R injury. This article systematically summarizes the generation and physiological effects of endogenous hydrogen sulfide, as well as its protective mechanisms in different systems such as the heart, brain, kidney, liver, retina, and testes. In addition, the clinical transformation prospects and current challenges of hydrogen sulfide in ischemia-reperfusion injury were discussed.

Key words: hydrogen sulfide,ischemia-reperfusion injury,antioxidant,Inhibition of apoptosis,Inhibition of inflammation

Introduction:

Over the years, hydrogen sulfide (H_2S) has been known for its rotten egg like odor, toxicity and environmental hazard. The toxicological mechanism of H_2S is mainly to inhibit the cytochrome c oxidase in mitochondria, thus causing chemical asphyxia of cells[1, 2]. Cytochrome c oxidase (COX) is an important electron transmitter in the respiratory chain, which participates in the process of cellular respiration. Its activity is inhibited, which reduces the utilization of oxygen in mitochondria, leading to cell hypoxia[3, 4]. In recent years, human understanding of H_2S has gradually shifted from toxic substances to gas transmitters with therapeutic drug potential. In 1989, hydrogen sulfide was proven to exist in the human brain and may play a certain physiological role[5]. In 1996, Japanese scientists demonstrated that hydrogen sulfide is a potential signaling molecule that can be produced by Cystathionine-β-synthase (CBS) and involved in neurotransmission[6]. The following year, they discovered that Cystathionine-γ-lyase (CSE) is another enzyme that produces[7]. Subsequently, Wang et al. confirmed that hydrogen sulfide is the third physiological signaling molecule, except for carbon monoxide (CO) and nitric oxide (NO)[8]. Since then, the field of sulfide research has developed rapidly and the research results have become richer,In a 2005 paper, Blackstone et al. reported in a pioneering manner that H_2S can induce a reversible pseudo-death-like state in mice. They hypothesized that H_2S-mediated induction of pseudo-death may have beneficial medical applications, such as ischemia-reperfusion (I/R) injury or organ preservation after trauma[9].

Ischemia reperfusion injury (IRI) is a special pathological phenomenon characterized by the sudden aggravation of tissue damage, or even irreversible damage, after a certain period of tissue ischemia restores blood supply[10, 11]. As the name suggests, I/R injury can be divided into two stages. Ischemic stage refers to the restriction of blood supply to tissues or organs, which is generally caused by embolus blocking arteries, causing imbalanced tissue metabolism, leading to severe tissue hypoxia and microvascular dysfunction. The subsequent tissue reperfusion stage will further enhance the activation of programmed cell death, congenital and adaptive immunity[12-14]. The tissue damage caused by IRI will greatly increase the incidence rate and mortality of some diseases, such as acute myocardial infarction, ischemic stroke, acute renal injury, intestinal obstruction, hyperkalemia and multiple organ failure, and also bring great challenges to surgical operations such as artery bypass grafting, limb replantation and organ transplantation[15, 16]. At present, there is still some controversy over the exact molecular mechanism related to the occurrence of IRI, and treatment strategies are also hindered. However, the gas mediated cellular signaling pathway may provide a new direction for its therapeutic strategy. Previous studies have found that NO and CO_2 have a protective effect on ischemia-reperfusion injury, and the role of hydrogen sulfide cannot be underestimated.

In this review, we will discuss the understanding of the protective mechanisms of H2S in different organs, especially the multifunctional advantages of this gas in vivo and its clinical potential in ischemia-reperfusion injury.

2. General physicochemical properties of hydrogen sulfide

Hydrogen sulfide is a colorless and highly toxic flammable gas, with its unique odor being the smell of rotten eggs or the smell of decaying sewage. Its molecular weight is 34.08, and its vapor density is heavier than air, making it easier to diffuse at lower points[17, 18]. As a binary weak acid, hydrosulfuric acid is an aqueous solution of H_2S that can reach dissociation equilibrium at room temperature (25). The solution concentration in a saturated state is 0.11mol.dm^{-3}, and its pH value is approximately 4.0. At 37 and pH 7.4, pK α 1=6.76, there is about 20% H_2S, 80% HS^- and a small amount of negligible S^{2-} in extracellular fluid[19]. At the same time, H_2S is also a small gas molecule with high lipophilicity, which allows it to freely pass through the Lipid bilayer structure of the cell membrane[20]. Hydrogen sulfide is a compound similar to water molecules that can be oxidized into sulfur dioxide, sulfate, thiosulfate, and elemental sulfur. In the body, H_2S can be oxidized to sulfates and thiosulfates, which can be excreted in the urine. Some studies suggest that urinary thiosulfates can serve as one of the biomarkers of hydrogen sulfide poisoning[17, 21].

3.Production and metabolism of hydrogen sulfide

3.1Production of endogenous hydrogen sulfide

In mammalian cells, enzyme catalysis and non enzyme catalysis are two ways to produce endogenous hydrogen sulfide. Some studies have shown that enzyme catalysis is the main production route, and CBS, CSE and MST are the three key enzymes of this route[22-24].

Both CBS and CSE use pyridoxal phosphate (also known as vitamin B6) as cofactors, and their concentrations vary in different tissues[25, 26]. CBS mainly exists in the central nervous system (cerebellum, hippocampus) and liver tissue[27]. CSE mainly regulates H_2S in cardiovascular system and respiratory system[28]. These two enzymes are only present in the cytoplasm and catalyze the conversion of homocysteine to cysteine, generating H_2S, by participating in the reverse sulfur conversion pathway. Research has found that MST is also an enzyme involved in endogenous H2S production[29]. Unlike the two enzymes mentioned earlier, the cofactor of MST is zinc (Zn)[17]. It often co catalyzes with cysteine aminotransferase (CAT) in mitochondria to produce hydrogen sulfide, L-cysteine, and α-Ketoglutaric acid generates 3-mercaptopyruvic acid (3-MP) under the catalysis of CAT, and then generates hydrogen sulfide and pyruvic acid under the action of 3-MST[30]. In 2013, a new enzyme catalysis pathway was proposed by Japanese scientists[31]. This pathway occurs in peroxisome. D-amino acid oxidase (DAO) catalyzes D-cysteine to produce 3-MP, and then the product is transported to mitochondria through vesicles to participate in the next reaction[32-34]. Endogenous hydrogen sulfide enzymatic generation pathway (as shown in Figure 1). Some studies have found that when the human body is in the state of oxidative stress or hyperglycemia, the hydrogen sulfide produced through non enzyme catalysis will greatly increase. In red blood cells, the reduction equivalent produced by glucose oxidation can be utilized to reduce elemental sulfur or polysulfides to hydrogen sulfide[17].

Figure 1

3.2 Metabolism of endogenous hydrogen sulfide

In mammals, hydrogen sulfide is excreted differently in different systems. In the respiratory tract, hydrogen sulfide is directly excreted in the form of gaseous molecules; Through the urinary tract, H_2S is mainly excreted in the form of thiosulfate or free sulfate in the urine. However, in the gastrointestinal tract, most hydrogen sulfide is still excreted in the form of free sulfide in the feces[17]. H_2S mainly has the following three metabolic pathways:1). The elimination of hydrogen sulfide through the mitochondrial sulfide oxidation pathway, with sulfoquinone oxidoreductase (SQOR) being the key enzyme in this reaction. Firstly, hydrogen sulfide is oxidized to thiosulfate under the catalysis of SQOR[35, 36]. In this reaction, the main sulfur acceptor is glutathione (GSH), and the resulting product is glutathione disulfide (GSSH)[37, 38]. In the next step of the reaction, rhodanese (orTST) plays a crucial role as a sulfur transferase that can further oxidize thiosulfate to sulfite or sulfate[39, 40]. However, due to the rapid oxidation of sulfite to sulfate, hydrogen sulfide is ultimately expelled from the body in the form of thiosulfate or sulfate through this pathway[17, 40]. 2). Research has found that methylation occurring in the cytoplasm is another metabolic pathway for hydrogen sulfide[24].

Thiol-S-methyltransferase (TSMT) can catalyze the conversion of hydrogen sulfide to methyl mercaptan and dimethyl sulfide. TSMT is commonly present in cells in the human body, but has high activity in mucosal cells of the colon and cecum[41]. Compared to the sulfide oxidation pathway, the metabolic process of sulfide methylation is slower. In a study, the rate of sulfide methylation in mammalian colon mucosal cells was approximately 10000 times slower than the oxidation rate of H_2S[42]. 3). Hydrogen sulfide can be cleared by methemoglobin, metal containing or sulfur containing macromolecules. Methemoglobin and myoglobin can promote the binding of hydrogen sulfide and iron by regulating the reactivity of iron, accelerating the oxidation rate of hydrogen sulfide[43].

Figure 2

4.H_2S honer

4.1 Sulfates

Sulfalts are currently the most common hydrogen sulfide donors in biological research, such as sodium sulfide and sodium hydrosulfide, which have been shown to have protective effects on cells in disease states in multiple studies[44]. Both sodium sulfide and sodium hydrosulfide exhibit crystalline powder appearance, which is easily soluble in water and can provide hydrogen sulfide more directly. In early studies, Wang et al. used NaHS aqueous solution to release H_2S and found that it can reduce systemic arterial pressure, indicating that hydrogen sulfide has the characteristic of relaxing blood vessels[45]. This has been verified in the research of Daniel et al., in addition, they also found that the reduction of hydrogen sulfide donors will lead to the reduction of cardiac output, which will lead to the reduction of systemic arterial pressure, and this phenomenon does not depend on the regulation of the central nervous system[46]. In multiple studies, hydrogen sulfide released by exogenous donor NaHS can play a protective role in organ damage, such as myocardial damage[47, 48],liver[49],brain[50],kidney[48]et. However, the chemical properties of sulfide salts are not stable, and the dosage and speed of hydrogen sulfide produced after direct dissolution in water are uncontrollable. The release of a large amount of hydrogen sulfide can cause a sudden drop in blood pressure, which has adverse effects on experimental animals.

4.2 Lawesson reagent and their derivatives

Lawesson reagent (LR) is a common and readily available sulfur ion agent that can serve as a hydrogen sulfide releaser (H_2S releaser). The molecule of Lawson reagent contains a quaternary ring with alternating sulfur and phosphorus atoms. Under high temperature conditions, the sulfur/phosphorus quaternary ring opens to form two unstable dithiophosphines (R-PS2), which decompose and release H_2S[51, 52]. Compared to sulfide salts, LR releases hydrogen sulfide more slowly[52]. However, the detailed release molecular dynamics of LR are still unclear and lack water solubility, so it has not been widely used as a hydrogen sulfide donor. morpholin-4-ium 4 methoxyphenyl (morpholino) phosphinodithioate (GYY4137) is a new water-soluble hydrogen sulfide donor synthesized based on LR reagent, which can slowly release hydrogen sulfide. Some studies have found that GYY417 has the function of dilating blood vessels to resist hypertension[53]. Not only that, it can also exert myocardial protection and prevent myocardial ischemia and reperfusion injury by inhibiting inflammation, reducing cell apoptosis, and reducing ROS production[54, 55]. In addition to its myocardial protective effect, some scholars have found that in ischemia-reperfusion injury, GYY4137 increases antioxidant activity by activating the Nrf2 signaling pathway, which can effectively alleviate renal injury[56]. This protective effect has also been reported in testicular torsion and intestinal injury[57, 58].

4.3 STS (Sodium Ihiosulfate-Supplemented)

Sodium thiosulfate is also a water-soluble hydrogen sulfide donor with minimal side effects, and its chemical formula is $Na_2S_20_3$. STS is an antidote that has been approved by the FDA and is currently mainly used in clinical practice to treat calcification reactions and toxic reactions (such as cisplatin poisoning, CO poisoning, cyanide poisoning, etc.)[59-61]. As mentioned earlier in the metabolism of hydrogen sulfide, hydrogen sulfide can be oxidized to thiosulfate, and in turn, STS can also become a source of hydrogen sulfide. When the body is in a state of hypoxia, hydrogen sulfide can be regenerated in thiosulfate through 3-MST and rhodase[62].

In addition to releasing hydrogen sulfide, STS is also an effective antioxidant that has been proven to have strong protective effects in different organ injuries, such as acute liver injury[63], acute lung injury[64], brain injury caused by I/R[65], myocardial injury[66],, kidney injury[67], etc.

Studies have shown that STS may have anti-inflammatory effects and protect vascular endothelial cells. Hydrogen sulfide seems to be able to inhibit NF-ϰB signaling pathway exerts anti-inflammatory effects[68]. Because of these cytoprotection on I/R injury, STS therapy has great potential in organ transplantation. The organ preservation solution added with STS is expected to become a simple, cheap and safe new treatment strategy, which can reduce the transplant sequelae and improve the success rate[69].

4.4 Natural hydrogen sulfide donors and derivatives

Some natural foods can also serve as donors of hydrogen sulfide. Garlic is considered a good preventive food and has been found to have great medicinal research value[70, 71]. Allicin is a metabolic active substance in garlic, which can be decomposed to produce diallyl polysulfides, such as diallyl sulfides (DAS), diallyl disulfides (DADS) and diallyl trisulfides (DATS)[72].And these sulfides can react with thiol groups (glutathione) to produce hydrogen sulfide[73]. However, due to the rapid release of hydrogen sulfide in water by DATS, some laboratories have utilized exploiting mesoporous silica nanoparticles(MSN)as a carrier to construct a new H_2S release system (DATS-MSN)[74]. DATS-MSN can release H_2S more slowly and controllably. In this study, compared to traditional H_2S donors (NaHS, DATS, and GYY4137), DATS-MSN showed better cardioprotective effects[74].

4.5 AP39

In addition, a H_2S donor targeting mitochondria (AP39) has been synthesized by scientists. 10-oxo-10-(4-(3-thioxo-3H-1,2-dithiol-5yl)phenoxy)decyl (AP39) can reduce intracellular oxidative stress and pro-inflammatory factor gene expression, maintain cell vitality, ensure mitochondrial energy and DNA integrity, and play an anti-inflammatory and antioxidant cytoprotection[75]. In mouse heart transplantation experiments, studies have found that adding AP39 to organ preservation solution can significantly improve cell viability, reduce cold ischemia-reperfusion injury, and tissue fibrosis[76]. In mouse pancreatic transplantation experiments, AP39 can significantly reduce ROS production and improve pancreatic island function[77]. These studies undoubtedly demonstrate the significant potential of AP39 in preventing and treating I/R injury in organ transplantation. As an H_2S donor, in addition to protecting cells, AP39 can induce vascular relaxation by stimulating NO signaling and activating K_{ATP} channels (Kchannels)[78]. The development of AP39 shows that the development of specific target donors of hydrogen sulfide in subcellular organelles has great potential in future biological research.

The mechanism of ischemia-reperfusion

According to the progression of diseases, ischemia-reperfusion injury can be divided into two stages: ischemia and reperfusion. It is generally believed that the degree of cell dysfunction, injury, and necrosis is related to the severity and duration of ischemia. Therefore, the main idea for treating I/R is to restore blood flow to the ischemic site as soon as possible[13]. However, the sensitivity of different organs to ischemic manifestations also varies, such as the brain, heart, and other organs with poor tolerance to ischemia and hypoxia, and differences in organ tolerance can also affect the degree of cell damage. In addition, although the recovery of reperfusion can provide oxygen and nutrients to cells, it will further strengthen the damage after ischemia, activate cell death and immune response, etc[12]. On the other hand, inflammatory mediators will also be transported to the distal organs with the recovery of reperfusion, which is also the reason for multi organ failure in the later stage of I/R[79-81]. I/R is a dynamic process with significant differences in organs, so a deeper understanding of its molecular mechanisms can help us find better treatment methods.

Calcium overload

When ischemia occurs, ATP in cells is rapidly depleted, ATP synthesis decreases, sodium pump activity decreases, intracellular Na^+ content increases, and sodium calcium exchange proteins are activated, leading to reverse transport of Na^+ to the extracellular space and an increase in intracellular Ca^{2+}[82, 83]. On the

other hand, due to hypoxia and anaerobic metabolism, the production of H^+ increases, and the pH of extracellular fluid and cytoplasm decreases. When tissue perfusion resumes, the pH of extracellular fluid increases, but the pH of cytoplasm is still very low. In order to reduce the accumulation of H^+ in cells, H^+-Na^+ exchange protein and Na^+-Ca^{2+} exchange protein are activated, increasing calcium overload[82]. When the body is in a state of stress, the release of a large amount of catecholamines activates protein kinase C(PKC) through a signaling pathway, promotes H^+-Na^+ exchange, and also increases intracellular Ca^{2+}. Due to the massive accumulation of Ca^{2+}, the damage of endoplasmic reticulum and mitochondria intensifies. With the complete opening of the mitochondrial mPT pore(mitochondrial permeability transition pore), it will have a more negative impact on cells[84].

Figure 3

5.2 ROS

When ischemic tissue undergoes reperfusion, blood brings oxygen and nutrients to the tissue. At the same time, due to the low concentration of antioxidants in cells, the production of reactive oxygen species (ROS) increases. In the I /R process of biology, ROS will be produced by many ways, including mitochondrial electron transfer chain (ETC), xanthine oxidase system (XOD), NADPH oxidase system and nitric oxide synthase (NOS), etc[85]. The first three are related to oxidative stress in multiple organs, such as the heart, brain, lungs, liver, pancreas, kidneys, and gastrointestinal tract[86]. NOS mainly acts as an oxidative stress factor in vascular endothelial cells[87]. During the metabolism of normal mitochondria, the respiratory chain complex on the inner mitochondrial membrane can produce a small amount of ROS[88]. As mentioned earlier, when I/R occurs, due to hypoxia, changes in ATP, pH, and calcium overload occur in cells, which can lead to mitochondrial damage and produce more ROS. However, ROS further exacerbates oxidative stress, leading to a vicious cycle of cells[82, 88].

The xanthine oxidase (XOD) system is an important pathway for ROS production. Under ischemia, ATP synthesis is reduced and xanthine dehydrogenase (XDH) is converted into xanthine oxidase (XOD). At the same time, ATP degradation products (ADP, AMP, hypoxanthine) accumulate. When reperfusion is resumed, a large amount of oxygen molecules enter the tissue with the blood, and XOD catalyzes the conversion of hypoxanthine into xanthine and uric acid, producing a large amount of ROS[89]. The oxygen free radicals generated by this pathway have chemotactic effects, attracting and activating a large number of white blood cells to aggregate. When the tissue resumes oxygen supply, the activated white blood cells' oxygen consumption increases sharply, further producing a large amount of oxygen free radicals, causing cell damage.

The NOx/Deox family of NADPH oxidase mainly includes 7 subtypes, such as Nox-1, Nox-2, Nox-3, Nox-4, Nox-5, Duox-1 and Duox-2, these enzymes have the ability to produce ROS[90]. Under hypoxic conditions, hypoxia inhibitory factor-1α (HIF-1α). Promote the activation of NOX enzyme, and after reperfusion, cells will release some chemical factors to further activate NADPH oxidase, such as phospholipase A2 (PLA2), TNF-α, IL-1β, IFN-γ and angiotensin II(Ang II), etc. Overexpression of NADPH oxidase after activation enhances ROS production[91, 92].

In addition to the aforementioned pathways, NOS is also an important pathway for generating ROS. Tetrahydrobiopterin (BH4) is a cofactor of NOS enzyme. In I/R, oxidative stress oxidizes BH4 to BH2, leading to a decrease in BH4 cell level and uncoupling of NOS, thereby promoting ROS production[93].

5.3 Cell death

The I/R process of organisms is dynamic, and the mechanism for producing ROS is also complex. The ROS produced by the above pathways may accumulate in cells during the ischemic stage and inhibit antioxidants. However, after tissue restoration of blood supply, if ischemia is severe, ROS induced oxidative stress may further cause cell damage and even cell death[94].

Apoptosis is a process of programmed cell death, mainly caused by calcium overload and ROS activation in I/R. There are two pathways of cell apoptosis that can interact with each other: endogenous apoptosis

pathway and exogenous apoptosis pathway. Endogenous pathway, also known as mitochondrial pathway. In the cells injured by ischemia/reperfusion, a large amount of calcium influx and ROS production will cause the opening of mitochondrial mPT pore and the activation of apoptosis promoting Bcl-2 family, increase the permeability of mitochondrial membrane, release cytochrome C into the cytoplasm, and then combine with apoptosis protease activating factor 1 (APAF-1) to activate Caspase-9 and form a complex, and then trigger the apoptosis cascade reaction to promote apoptosis[95].The exogenous pathway, also known as the death receptor pathway, is mainly activated by death factors or receptors. Important death factors mainly include TNF-α,Fas ligands, TRAIL, and TL1A. As mentioned earlier, during I/R, reperfusion cells release TNF-α,Activate the JNK pathway to stimulate the production of ROS. The accompanying oxidative stress will further stabilize the phosphorylation of c-JunN-terminal kinase and accelerate cell death[96]. If TNF-α Persistent increase will induce the TNFR related death domain (TRADD) to combine with it to synthesize TNF α- TRADD. TNF α- TRADD and Fas FADD can induce and activate caspase 8 and 10, then enzymolysis activates downstream caspase 3, 6 and 10, and then starts the process of cell apoptosis[97]. However, in ischemia-reperfusion injury, cell apoptosis is not as common as necrosis mentioned below.

Necrotizing apoptosis is also a type of programmed cell death, but its impact on organisms is completely different from previous cell apoptosis. The main characteristics of necrotic apoptosis are cell swelling, disintegration of organelle and leakage of intracellular components, which often cause severe inflammatory reaction in ischemic tissues[98, 99]. As a regulatory mode of death, the main factors triggering necrotic apoptosis are the interacting serine threonine kinase 3 (RIPK3) and mixed lineage kinase like domain (MLKL)[100]. RIP3 can enable TNF-α driven cell death changes from apoptosis to necrotic apoptosis. When Caspase-8 is depleted or cIAP is deficient, TNFR1 will promote necrotic apoptosis[99]. The assembly of necrotic complex is mainly related to RIPK1/RIPK3 interaction and MLKL activation. RIPK3 induces phosphorylation of MLKL, leading to oligomerization and translocation of MLKL to the lobules within the plasma membrane, ultimately increasing plasma membrane permeability and cell death[100]. ROS induced DNA damage also promotes the formation of necrotic complex by activating poly(ADP-ribose)polymerase (PARP), further accelerating cell death. Due to the close relationship between necrotic apoptosis and the occurrence of inflammation in the human body, understanding the molecular mechanism and pathophysiological significance of necrotic apoptosis remains an important goal of therapeutic I/R research.

The role of autophagy in I/R is bidirectional, which can both protect cells and disrupt them. During ischemia, appropriate mitochondrial autophagy can clear partially damaged mitochondria and reduce subsequent damage[101].During the reperfusion phase, the levels of $Ca^{2+}$and ROS increase in the cells, while oxidative stress inhibits the activity of rapamycin mTOR, leading to the formation of ULK-1 complexes and PI3K III class, which induce autophagy. However, autophagy cannot clear all damaged mitochondria, and when autophagy clearance capacity is exceeded, it can lead to cell death[102, 103].

5.4 Inflammation

During reperfusion, the production of a large amount of ROS activates the NF-ϰB gene, further stimulating the secretion of TNF-α by endothelial cells and macrophages[104]. On the one hand, TNF-α can induce cell apoptosis through sphingosine dependent mechanism. On the other hand, it can also cause leukocyte infiltration in damaged tissues, increase the permeability of vascular endothelial cells, produce no reflow phenomenon, and aggravate reperfusion injury[105, 106]. At the same time, activated cells release a large amount of inflammatory factors, such as IL-1, IL-6, IL-8, IL-10, IL-18, etc[107].

H2S and I/R injury6.1 Myocardial protective effect of H_2S

When the blood perfusion and oxygen supply of the myocardium are severely reduced, extensive cell death may occur, leading to myocardial infarction[108, 109]. As mentioned earlier, although restoring blood supply can alleviate ischemia to a certain extent, it can also lead to a series of more serious reactions, such as oxidative stress, cell damage, and even death. In current research on I/R, increasing evidence suggests that endogenous H_2S regulation or exogenous H_2S donors may be involved in the pathogenesis of ischemic cardiomyopathy, improving cardiac function, controlling structural lesions, and reducing related complications[110-112]. We

found that H_2S may have a protective effect on myocardial cells through the following five mechanisms.

6.1.1 Antioxidant

The massive production of ROS during reperfusion is the main cause of a series of oxidative stress responses, however, H_2S can inhibit its production by regulating ROS signaling pathways, such as inhibiting NF-ϰB and JAK2-STAT3 pathways to reduce ROS levels[113].At the same time, H_2S can also increase the expression levels of superoxide dismutase (SOD) and glutathione (GSH) in I/R tissues, both of which are antioxidant enzymes that protect cardiomyocytes by converting peroxides (H_2O_2)[74, 114]. In addition H_2S can promote nuclear translocation of nuclear factor-E2-related factor-2 (Nrf2), an important antioxidant transcription factor that increases transcription of antioxidant proteins and reduces apoptosis and mitochondrial damage[115].

6.1.2 Inhibition of apoptosis

In the process of apoptosis, Bcl-2 plays a crucial role. It has been reported that H_2S is able to reduce the proportion of apoptotic cells in the myocardium of I/R mice by upregulating the expression level of Bcl-2 and decreasing the expression of Bax and cystein 3[116]. Apoptotic proteins (IAPs) can block the apoptotic cascade response, and it has been found that H_2S can inhibit apoptosis by affecting the phosphorylation of IAPs and cysteine aspartase recruitment structural domains.

6.1.3 Autophagy

Hydrogen sulfide protects cardiomyocytes through a bidirectional action in autophagy[117]. Tissue or cellular ischemia leads to the development of cellular autophagy, and moderate cellular autophagy facilitates the repair of damaged cells. It has been demonstrated that hydrogen sulfide can exert cytoprotective effects by promoting autophagy, which seems to be associated with NLRP3 inflammatory vesicles. Excessive autophagy exacerbates cellular I/R injury, and H_2S can activate PI3K/SGK1/GSK3β signaling pathway and PI3K/Art/mTOR signaling pathway to inhibit autophagy and provide protection for I/R-injured cardiomyocytes[118, 119].

6.1.4 Inhibition of inflammation

In the current study, hydrogen sulfide can inhibit the inflammatory response of cardiomyocytes, which is one of the important mechanisms for its cardioprotective effect[120, 121]. In earlier years, some researchers found that certain H_2S donors can reduce leukocyte adhesion and infiltration, and this effect seems to be related to the activation of K_{ATP}channels[122, 123]. In addition to this, administration of H_2S treatment before the ischemic tissue regains blood supply also prevents the activation of NF-ϰB and reduces the production of pro-inflammatory mediators, with the most significant reduction of IL-1 and IL-6[124, 125]. Increased expression levels of TNF-α during reperfusion promote interaction between leukocytes and endothelial cells, resulting in increased infiltration of inflammatory cells in the I/R region of the myocardium, which leads to more severe myocardial injury, so inhibition of TNF-α expression may attenuate myocardial injury. It has been found that H_2S can inhibit the adhesion of inflammatory cells and the release of associated inflammatory factors caused by TNF-α activation, significantly reducing the expression levels of chemotactic protein-1 (MCP-1), adhesion factors, etc[126].

6.1.5 Protection of mitochondria

The role of mitochondria is particularly important in mammalian growth and development, providing energy for the basic metabolism of the body. When myocardial I/R occurs, the function of mitochondria is severely impaired, leading to further myocardial damage. It has been found that NaHS can reduce mitochondrial malondialdehyde levels in ischemic cardiomyocytes, while elevating the activities of superoxide dismutase and glutathione peroxidase, allowing the preservation of mitochondrial function[127]. In addition, H_2S also increased the efficiency of complexes I and II of the oxidative respiratory chain in mitochondria and inhibited cytochrome oxidase, reducing the metabolism of cardiomyocytes to a preconditioned state, thereby reducing cardiomyocyte damage[128, 129].

6.2 Neuroprotective effects of hydrogen sulfide

Ischemia-reperfusion injury of the brain is an important cause of ischemic stroke, mainly manifested by necrosis or softening of ischemic brain tissue and focal neuronal damage[130, 131]. Stroke is the most common cause of disability in developed countries, and its high morbidity and mortality pose a great threat to the health of the whole population[132, 133]Therefore, it is particularly important for researchers to find ways to detect and prevent ischemic strokes early. Fortunately, it has been found that appropriate concentrations of H_2S have a neuroprotective effect in I/R injury in brain tissue[134, 135]. Many experimental data suggest that the use of H_2S donors to provide low concentrations of H_2S can reduce infarct size and restore neurological function in brain tissue through mechanisms such as antioxidant, anti-inflammatory, anti-apoptotic, modulation of autophagy, protection of mitochondrial function and vasodilation and vasogenesis[136-139]. In addition, it has been reported that H_2S can also reduce infarct size and restore neurological function by modulating the expression of N-methyl-D-aspartate receptor (NMDA) receptor 亚expression levels, thereby activating the CREB pathway and improving neuronal cell survival[140, 141].However, another study showed that high concentrations of hydrogen sulfide inhibited cytochrome C oxidase activity in experimental mice, leading to brainstem toxicity and respiratory depression[142].These suggest that H_2S plays a dual biological role in the brain[143, 144] . Although the potential mechanisms of hydrogen sulfide in neuroprotection are still not well understood and refined, there is no doubt that as a multi-targeted neuromodulator, H_2S has a very bright application in the treatment of ischemic stroke.

Figure 4

6.3 Nephroprotective effects of hydrogen sulfide

Renal ischemia-reperfusion injury (IRI) is a major predisposing factor for the development and progression of acute kidney injury (AKI)[145, 146]. AKI is a complex clinical syndrome characterized by a rapid decline in renal function, such as decreased glomerular filtration rate (GFR) with increased creatinine and urea nitrogen, water-electrolyte disturbances, acid-base imbalance, oliguria or even anuria[147, 148].AKI is often associated with serious complications, and the high mortality rate places a significant burden on the healthcare system[149]. Some recent studies have shown that H_2S can improve renal function during IRI to prevent AKI, which seems to be associated with decreased levels of ROS expression[150-152]. In addition to antioxidant effects, H_2S may also exert renoprotective effects through several other mechanisms. First, H_2S can induce vascular relaxation through the opening of K_{ATP} channels in endothelial cells and renal vascular smooth muscle cells, thereby increasing renal blood flow[45, 153]. Second, it has been suggested that H_2S has the potential to protect renal function by inhibiting angiotensin (Ang) II in the RAAS system[154]. In addition, some investigators have also found that A39, a mitochondrial-targeting H_2S donor, can reduce ROS levels, protect mitochondrial function, and reduce renal epithelial cell injury, however, this protective effect is dose-dependent[155, 156].

6.4 Hepatoprotective effects of hydrogen sulfide

Ischemic liver tissue is extremely susceptible to more severe liver dysfunction and failure after reperfusion occurs[157, 158]. More seriously, hepatic ischemia-reperfusion(HIR) can also affect the success of liver resection or transplantation and increase the risk of death for the operator[157, 159]. The risk of death is increased. There is a lot of experimental data to demonstrate that H_2S can effectively protect liver tissue in hepatic I/R injury and is expected to be a new way to reduce the morbidity and mortality of hepatic I/R injury complications[160-162]. Some experiments have shown that the expression levels of endogenous H_2S and CSE are elevated in the tissues of HIR rats, and the researchers speculate that this may be due to the self-protective response of the organism induced by HIR. Meanwhile, after using the exogenous H_2S donor NaHS in HIR rats, the investigators found that NaHS could attenuate I/R-induced liver injury[160, 163] At present, there has been a large amount of data demonstrating that H_2S can play a role in reducing liver injury through various mechanisms, such as inhibition of oxidative stress, anti-apoptosis, anti-inflammation, protection of mitochondrial function and regulation of autophagy[164-169]. However, it has also been found that endogenous H_2S may exacerbate HIR-induced liver injury in the context of insulin resistance, so H_2S should be used with caution in this situation[170].

6.5 Retinal protective effect of hydrogen sulfide

I/R injury to the retina is the cause of many retinal vascular diseases, such as diabetic retinopathy (DR), glaucoma, retinal artery occlusion (RAO), etc[171]. It is mainly caused by the generation and accumulation of large amounts of ROS during ischemia and reperfusion, which causes a series of oxidative stress and inflammatory responses that promote irreversible damage to retinal ganglion cells, which may eventually lead to vision loss or even blindness[172]. In a study more than a decade ago, researchers injected an H_2S donor (ACS67) into the vitreous humor of rats with retinal I/R injury and subsequently found that ACS67 could regulate GSH levels and inhibit apoptosis of RGC-5 cells induced by oxidative stress, thus exerting a protective effec[173]. Another experiment found that direct inhalation of H_2S for pretreatment prior to retinal I/R injury in rats reduced the mortality of RGC[174]. In a 2016 study, it was first proposed that enzymes involved in the generation of H_2S and related pathways are activated during retinal IRI and may have the ability to induce retinal neovascularization[175]. In addition, H_2S may also protect retinal ganglion cells by inhibiting the production of inflammatory factors, activating signaling pathways involved in mediating protection of mitochondrial function and diastolic vascularity[176-178].

6.6 Testicular protective effect of hydrogen sulfide

Testicular torsion is a urological emergency that occurs in children and requires immediate surgical treatment; however, despite successful surgical intervention, the incidence of associated complications (such as testicular atrophy and infertility) ranges from 40-60%[179, 180]. Postoperative I/R injury is the main cause of testicular damage, and previous studies have demonstrated that testicular I/R injury is closely related to excessive production of ROS, with subsequent massive production of inflammatory factors, oxidative stress, and apoptosis further exacerbating tissue damage[181, 182]. The subsequent high production of inflammatory factors, oxidative stress and apoptosis further aggravate the tissue damage. In the last two years, studies have revealed that H_2S may have potential therapeutic effects in protecting testicular tissue[183, 184]. Bozkurt et al. first investigated the role of H_2S in I/R injury in testicular torsion and found that H_2S administration inhibited oxidative stress and suppressed the expression of TNF-α, Apaf-1, and iNOS to reduce tissue damage[184]. MPO, MDA and AOPP are markers of lipid peroxidation, and Yuksel et al. found that NaHS could effectively reduce the expression levels of MPO and AOPP. Meanwhile, Johnson scores were significantly higher in the H_2S administration group, suggesting that H_2S can improve spermatogenic function in I/R-injured testes[183].However, there are still relatively few related studies, and the mechanism of the protective effect of H_2S in testicular I/R injury is still unclear, and we need to conduct more in-depth studies.

DisscussionA growing body of evidence suggests that reasonable concentrations of hydrogen sulfide may play a powerful organ-protective role in ischemia-reperfusion injury, possibly acting primarily through mechanisms such as anti-apoptosis, modulation of autophagy, and inhibition of oxidative stress and inflammation. The growing understanding of the important biological effects of H_2S, such as vasodilatory, cytoprotective antioxidant and anti-inflammatory effects, as well as its signaling pathway mechanisms, has facilitated the translation of the highly promising cytoprotective functions of H_2S into more viable clinical therapeutic modalities. Key to this is the effective design of H_2S donors to deliver the desired therapeutic effects. As discussed earlier, designing stable, controlled H_2S donors that maintain a stable and slow release of H_2S over time is preferable for clinical applications, and much of the physiological utility of H_2S is derived from its redox properties. The uncontrolled and rapid release of H_2S donors rapidly alters the redox state of cells, and this alteration has a much greater impact on cells than its beneficial physiological functions. With rapidly increasing H_2S concentrations, the distribution of each different oxidation state sulfide is very different from the normal physiological state, yet each sulfide has its own unique physiological properties. The volatility of H_2S and its rapid metabolism make the development of H_2S donors uniquely challenging compared to the development of other small molecule donors, which are highly volatile and are always in a dynamic volatile-soluble equilibrium. In addition, many of the current H_2S donors are polysulfides, both the donor itself and the by-products of H_2S fraction production, so it is often difficult to distinguish whether the physiological effects of such donors are derived from H_2S or other polysulfides. another difficulty in H_2S research is how to quantify the range of endogenous H_2S concentrations during human circulation and the

changes in H_2S concentrations during treatment. This is mainly due to the reactive chemical nature of H_2S and the complex environment of sulfides in vivo. The inability to accurately monitor H_2S concentrations in the circulatory system or target organs will make it difficult to assess the exact relationship between H_2S and physiological effects. Therefore, it is important to develop methods that can quantitatively detect H_2S concentrations in vivo for H_2S research. In conclusion, although sulfide generators have not been new drugs to date, there is precedent for reducing metabolism and thus providing protection against I/R injury in humans. For example, hypothermia therapy has been shown to be beneficial for outcomes in a variety of situations, including out-of-hospital cardiac arrest and during myocardial revascularization. Although there are still many issues that need to be addressed, and these critical issues must be resolved to move into clinical treatment. However, future multidisciplinary collaborations involving nanomaterials, chemistry, pharmaceutical and biological disciplines may finally offer a possibility for H_2S therapy, and we look forward to seeing more interesting studies in this area.

Abbreviations

H2S: hydrogen sulfide, COX: Cytochrome c oxidase, CBS: Cystathionine-β-synthase, CSE: Cystathionine-γ-lyase, CO: carbon monoxids, IRI: ischemia-reperfusion injury, CAT: cysteine aminotransferase, 3-MP: 3-mercaptopyruvic acid, DAO: D-amino acid oxidase, SQQR: sulfoquinone oxidoreductase, GSH: glutathione, GSSH: glutathione disulfide, TSMT: Thiol-S-methyltransferas, LR: Lawesson reagent, GYY4137: morpholin-4-ium 4 methoxyphenyl (morpholino) phosphinodithioate, DAS: diallyl sulfides, DADS: diallyl disulfides, DATS: diallyl trisulfides, MSN: mesoporous silica nanoparticles, AP39: 10-oxo-10-(4-(3-thioxo-3H-1,2-dithiol-5yl)phenoxy)decyl, PKC: protein kinase C, ETC: electron transfer chain, XOD: xanthine oxidase system, ROS: reactive oxygen species, NOS: nitric oxide synthase, XDH: xanthine dehydrogenase, HIF-1α: hypoxia inhibitory factor-1α , PLA2: phospholipase A2, APAF-1: apoptosis protease activating factor 1, TRADD: TNFR related death domain, MLKL: mixed lineage kinase like domain, RARP: poly(ADP-ribose)polymerase, SOD: superoxide dismutase, Nrf2: factor-E2-related factor-2, MCP-1: chemotactic protein-1, NMDA: N-methyl-D-aspartate receptor, AKI: acute kidney injury, GFR: glomerular filtration rate, HIR: hepatic ischemia-reperfusion, DR: diabetic retinopathy, RAO: retinal artery occlusion.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

DDW and XYJ conceived and supervised the study. YQJ, HY, YFL, WG, YW, and XYL drafted the manuscript and prepared the figures. All authors read and approved the final manuscript.

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Figure legends

Figure 1. Endogenous hydrogen sulfide can be produced by two ways: Enzyme catalysis and non Enzyme catalysis. Enzyme catalysis is the main way and is catalyzed by four enzymes, such as CBS, CSE, MST and DAO. By Figdraw.

H2S: Hydrogen sulfide; CBS: cystathionine β-synthase; CSE: cystathionine γ-lyase; PLP: pyridoxal-5'-phosphate; 3-MST: 3-mercaptopyruvate sulfurtransferase; 3-MP: 3-methylpyridine; CAT: Cysteine aminotransferase; DAO:D-amino acid oxidase.

Figure 2. The H_2S oxidation pathway in mitochondria is mainly catalyzed by sulfuroquinone oxidoreductase. Finally, hydrogen sulfide is discharged from the body in the form of Thiosul-

fate or sulfate through this pathway. By Figdraw.H2S: Hydrogen sulfide; SQR: sulfuroquinone oxidoreductase; GSH: glutathione; GSSH: glutathione disulfide; TST: rhodanese; SDO: sulfide dioxygenase; Cyt c:cytochrome c oxidase; ATP: adenosine triphosphate; ADP:adenosine diphosphate; NADH: Nicotinamide adenine dinucleotide.

Figure 3.The mechanism of ion exchange leading to calcium overload during the ischemic and reperfusion stages. By Figdraw. ATP: adenosine triphosphate; CaBP: calcium binding protein; Na^{+}: sodium ion; Ca^{2+}: calcium ion; K^{+}: potassium ion; H^{+}: hydrogen ion.

Figure 4.H_2S can reduce the infarct size of cerebellar tissue and restore neurological function through mechanisms such as antioxidant, anti-inflammatory, anti-apoptotic, regulating autophagy, protecting mitochondrial function, and vasodilation and generation. By Figdraw. ATP: adenosine triphosphate; NF-ϰB: nuclear factor-kappa B; TNF-α: tumor necrosis factor-α· COX-2: cytochrome oxidase subunit 2; ROS: reactive oxygen species; iNOS: Inducible nitric oxide synthase;γ-GCS: γ-glutamylcysteine synthetase; VEGF: Vascular endothelial growth factor; mPTP: mitochondrial permeability transition pore.