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Review

Hydrogen sulfide and autophagy: A double edged sword

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ABSTRACT

Hydrogen sulfide (H_2S) has been considered the third gaseous signaling molecule that plays important roles in a wide range of physiological and pathological conditions. However, there has been some controversy on the role of H_2S in autophagy. Recent studies indicate that a number of signaling pathways are involved in the pro-autophagy effect of H_2S, such as PI3K/Akt/mTOR, AMPK/mTOR, LKB1/STRAD/MO25, and miR-30c signaling pathways. On the other hand, there are many signaling pathways that play important roles in the anti-autophagy effect of H_2S, including SR-A, PI3K/SGK1/GSK3β, PI3K/AKT/mTOR, Nrf2-ROS-AMPK, AMPK/mTOR, and JNK1 signaling pathways. Novel H_2S-releasing donors/drugs could be designed and identified in order to increase the therapeutic effects by mediating autophagy in human diseases. In this review, the H_2S metabolism in mammals is summarized and the effects of signaling pathways in H_2S-mediated autophagy are further discussed.

1. Introduction

Hydrogen sulfide (H_2S) has been recognized as the third gaseous signaling molecule, accompanying nitric oxide and carbon monoxide [1–3]. H_2S is produced endogenously in mammals from L-cysteine and homocysteine mainly by two pyridoxal-5′-phosphate (PLP)-dependent enzymes, termed cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE). Both CBS and CSE are cytosolic enzymes [3–5]. 3-mercaptopyruvate sulfurtransferase (3-MST), a PLP-independent enzyme, could act in combination with cysteine aminotransferase (CAT) to generate H_2S from L-cysteine in the presence of α-ketoglutarate. 3-MST and CAT are both located in the mitochondria and cytosol [3,6]. In addition, a recent study has demonstrated that D-amino acid oxidase could metabolize D-cysteine to an achiral α-ketoacid, 3-mercaptopyruvate, which is further metabolized to H_2S by 3-MST in both kidney and brain (Fig. 1) [7]. H_2S can be immediately released or stored in the forms of bound sulfane sulfur and acid-labile sulfur in the cells (Fig. 2A) [9–12]. Catabolism of H_2S is thought to occur via mitochondrial oxidation to thiosulfate and sulfate, scavenging by sulfhemoglobin, excretion from lung or kidney, and methylation by enzymes such as rhodanese and thiol methyltransferase to form dimethylsulfide and methanethiol (Fig. 2B) [13–15].

Autophagy, also known as macroautophagy, is a fundamental process by which cellular material is delivered to lysosomes for degradation and recycling [16]. Autophagy is involved in cellular and tissue homeostasis, physiology, development, and abnormalities in autophagy may contribute to many different pathophysiological conditions [17,18]. A number of studies have indicated that H_2S plays important roles in a wide range of physiological and pathological conditions, including glucose metabolism, energy production, ischemia-reperfusion (I/R) injury, vascular relaxation, angiogenesis, neuronal activity, and atherosclerosis [1,3,5,6,9,19–22]. However, there has been some controversy on the role of H_2S in autophagy. Recently, an increasing amount of evidence suggests that endogenously produced and/or exogenously administered H_2S could exhibit two obviously opposite effects on autophagy [23–26]. Therefore, it is urgent and essential to elucidate the mechanism of action of H_2S in the process of autophagy.

In this review, we highlight recent studies that provide new insight into the metabolism of H_2S in mammals, as well as further discuss the effects of signaling pathways in H_2S-mediated autophagy.

2. The pro-autophagy effect of H_2S

Accumulating evidence indicates that a number of signaling pathways are involved in the pro-autophagy effect of H_2S (Fig. 3), such as phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB/Akt)/mammalian target of rapamycin (mTOR) signaling pathway, adenosine monophosphate-activated protein kinase (AMPK)/mTOR signaling pathway, liver kinase B1 (LKB1)/sterile-20-related adaptor (STRAD)/mouse protein 25 (MO25) signaling pathway, and micro ribonucleic acid (RNA)-30c (miR-30c) signaling pathway.

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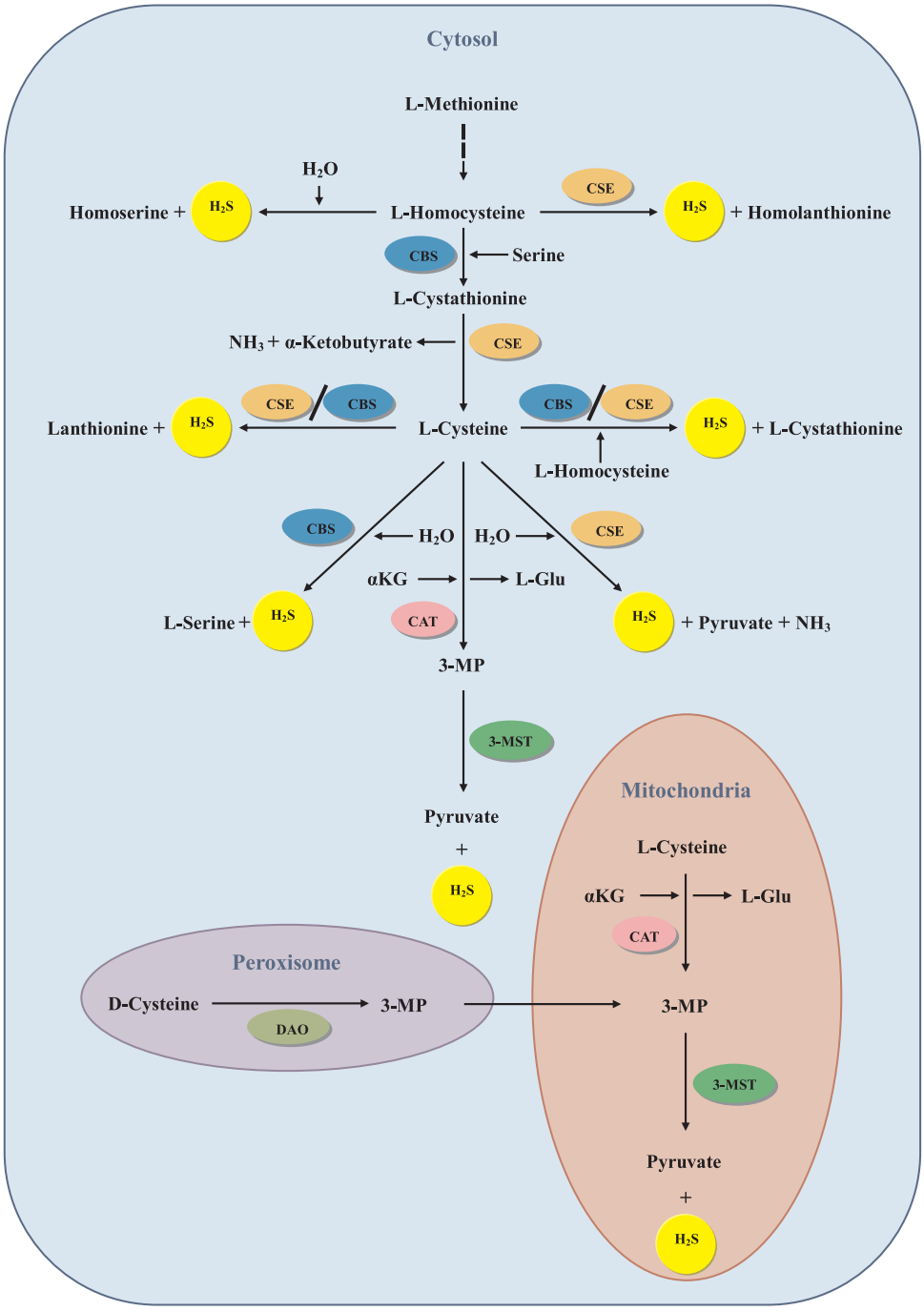

Fig. 1. A schematic illustration of the enzymatically-produced H_2S in mammals [8]. H_2S, hydrogen sulfide; H_2O, water; CSE, cystathionine γ-lyase; CBS, cystathionine β-synthase; NH_3, ammonia; αKG, α-ketoglutarate; L-Glu, L-glutamate; CAT, cysteine aminotransferase; 3-MP, 3-mercaptopyruvate; DAO, D-amino acid oxidase; 3-MST, 3-mercaptopyruvate sulfurtransferase.

2.1. PI3K/Akt/mTOR signaling pathway

In mammal cells, the PI3K/AKT/mTOR is an important signaling pathway that coordinates many cell activities [27]. It plays critical roles in the survival, proliferation, and growth of malignant cells and is involved in a number of studies in recent years [28–30]. The PI3K/AKT/mTOR pathway is one of the most frequently dysregulated signaling cascades in a wide variety of different neoplasms, which has made it a much desired target for pharmacologic intervention [31]. Treatment with 10^{-3} M sodium hydrosulfide (NaHS) (a donor of H_2S) for 24 h could inhibit human hepatocellular carcinoma cell migration, proliferation and cell division, as well as induce cell autophagy by inhibiting the PI3 K/AKT/mTOR signaling pathway [32]. Previous studies have indicated that autophagy acts as a double-edged sword in tumor growth and development in different experimental settings [32–35]. A recent review suggests that endogenous H_2S or treatment with relatively low levels of H_2S for a relatively short duration could maintain or promote cancer cell growth, while treatment with relatively high concentrations of H_2S donor for a relatively long period of time may exhibit anti-cancer effects [36]. Whether endogenous H_2S or treatment with relatively low levels of H_2S could inhibit autophagy through activating the PI3K/AKT/mTOR signaling pathway needs to be further clarified.

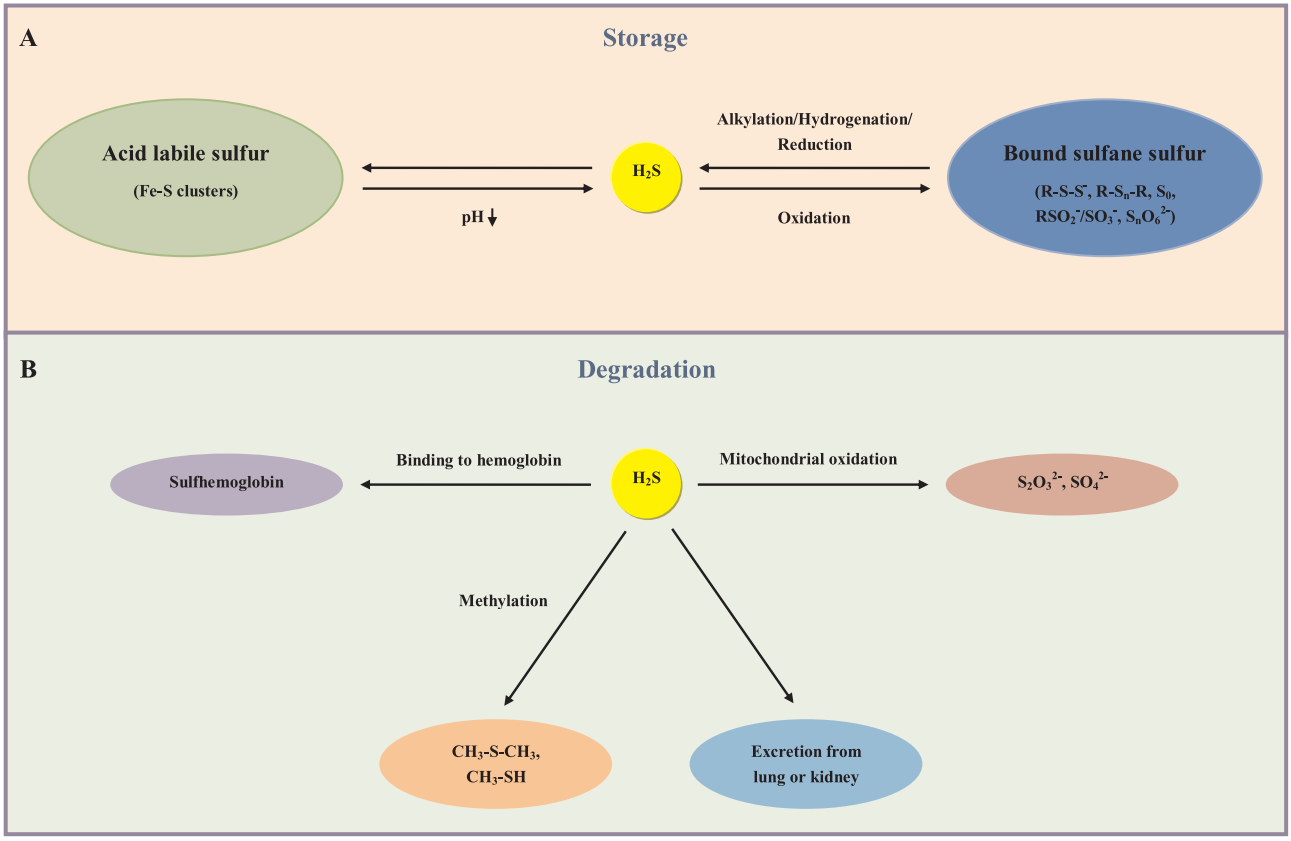

Fig. 2. A schematic illustration of the storage and catabolism of H_2S in mammals [8]. (A) H_2S can be stored as bound sulfane sulfur and acid-labile sulfur in the cells. (B) Catabolism of H_2S is thought to occur mainly via methylation, mitochondrial oxidation, binding to hemoglobin, and excretion from lung or kidney. H_2S, hydrogen sulfide; pH, potential of hydrogen; $S_2O_3^{2-}$, thiosulfate; SO_4^{2-}, sulfate; CH_3-S-CH_3, dimethylsulfide; CH_3-SH, methanethiol.

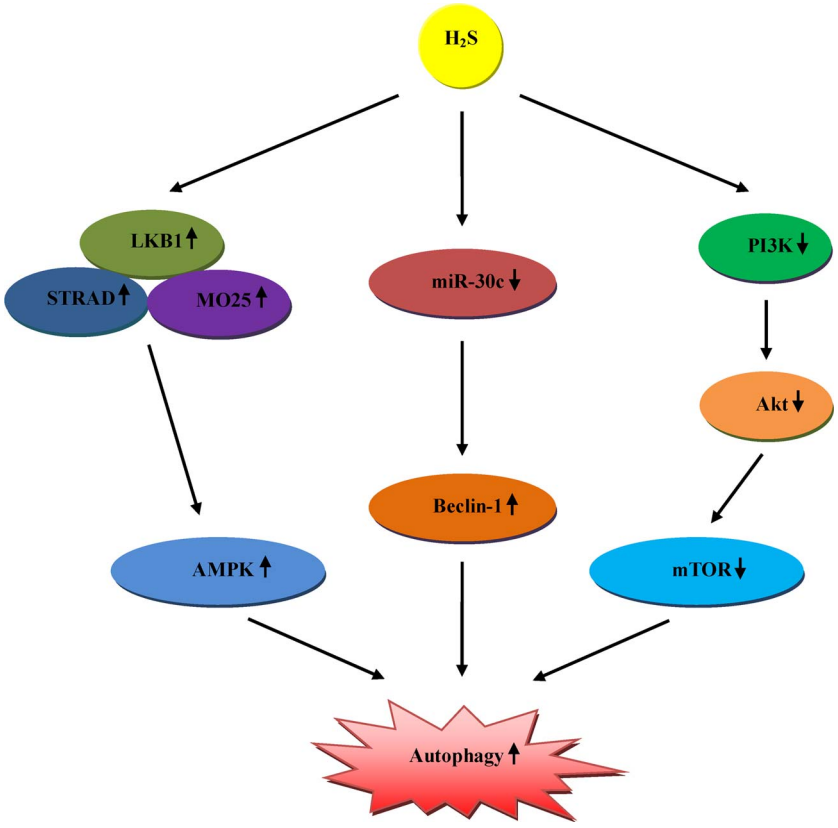

Fig. 3. A schematic illustration of the signaling pathways involved in the pro-autophagy effect of H_2S [8]. H_2S, hydrogen sulfide; LKB1, liver kinase B1; STRAD, sterile-20-related adaptor; MO25, mouse protein 25; miR-30c, micro ribonucleic acid (RNA)-30c; PI3K, phosphatidylinositol 3-kinase; Akt (PKB), protein kinase B; mTOR, mammalian target of rapamycin; AMPK, adenosine monophosphate-activated protein kinase.

Table 1
H_2S induces autophagy via the AMPK/mTOR signaling pathway.

Experimental models	Effects	Proposed mechanisms	Refs.
Colon epithelial cells (Human)	Treatment with NaHS (1 mM) for 24 h inhibits the proliferation of normal and cancerous colon epithelial cells	Inducement of the protective autophagy via the AMPK/mTOR cascade	[42]
Myocardial I/R *in vivo* (Rat)	ADT (a slow-releasing H_2S donor, 50 mg/kg, after reperfusion) protects against myocardial I/R injury	Probably through the activation of AMPK to restore autophagic flux	[43]
Acute pancreatitis (AP) (Rat)	Treatment with NaHS (100 μM, before AP induction) for 30 min exacerbates taurocholate-induced AP	Over-activating autophagy via AMPK/mTOR pathway	[44]
Nonalcoholic fatty liver disease (NAFLD) (Mouse)	Treatment with NaHS (56 μmol/kg/day) for 6 weeks could reduce serum triglyceride level and ameliorate NAFLD	Activation of liver autophagy via the AMPK-mTOR pathway	[45]
Diabetic cardiomyopathy (Rat)	Treatment with NaHS (100 μM) for 4 and 8 weeks protects against diabetic cardiomyopathy	Activation of autophagy via the AMPK-mTOR pathway	[46]
Myocardial I/R *ex vivo* (Rat)	Treatment with NaHS (10 μM, at the onset of reperfusion) for 10 s (6 times) could restore cardioprotection from post-conditioning	Up-regulation of autophagy via activation of AMPK/mTOR pathway	[47]
Brain of Zucker diabetic fatty (Rat)	Treatment with NaHS (50 μM, every 10 h for two days) protects against protein aggregation in diabetic brain	Up-regulation of autophagy probably through inhibition of the mTOR pathway	[48]

2.2. AMPK/mTOR signaling pathway

AMPK is involved in the regulation of metabolic energy balance at the whole-body level by responding to hormonal and nutrient signals, which could lead to changes in energy homeostasis [37,38]. Once activated, AMPK phosphorylates downstream substrates to inhibit anabolic processes and promote catabolism, resulting in adenosine 5′-triphosphate production and energy restoration [39,40]. mTOR is a serine/threonine protein kinase of the PI3K-related family that regulates cellular growth and metabolism in response to nutrient and hormonal cues [41]. A number of studies have indicated that AMPK/mTOR pathway is involved in the regulation of autophagy. As shown in Table 1, H_2S could activate autophagy via the AMPK/mTOR pathway. Therefore, AMPK/mTOR pathway may be a promising target in treating several diseases, such as myocardial I/R injury, acute pancreatitis, and diabetes.

2.3. LKB1/STRAD/MO25 signaling pathway

The LKB1/STRAD/MO25 complex contributes to a number of signaling pathways involved in metabolism and cellular proliferation [49]. In addition, the LKB1/STRAD/MO25 pathway seems to be conserved in regulating cell polarity [50,51]. LKB1 could phosphorylate and activate AMPK and AMPK-related kinases in an energy stress-independent manner [52,53]. AMPK in turn inactivates mTORC1 directly by phosphorylating the raptor and indirectly by phosphorylating the tuberous sclerosis complex 2, ultimately resulting in the induction of autophagy [52,54]. A recent study shows that treatment with 30 μM NaHS for 24 h mediates the beneficial effects in high glucose-treated mouse glomerular endothelial cells by induction of autophagy and regulation of matrix metabolism through the LKB1/STRAD/MO25 signaling pathway [55]. Many studies indicate that H_2S mediates the activation of AMPK via calmodulin kinase beta (CamKKβ) in rat glomerular epithelial cells, BV2 mouse microglial cells, and C2C12 mouse skeletal muscle cells [56–58]. Whether H_2S could induce cell autophagy through CamKKβ/AMPK pathway remains to be investigated.

2.4. MiR-30c signaling pathway

MicroRNAs (miRNAs) are non-coding RNAs of 19–22 nucleotides that are essential for development and homeostasis in diverse species [59,60]. miRNAs bind to the 3′-untranslated region of target mRNAs, forming an RNA-induced silencing complex that reduces protein synthesis by augmenting mRNA degradation or by diminishing translation [61–63]. miR-30c, a member of the miR-30 family, is evolutionarily conserved in many species [63]. miR-30c has been proved to regulate cisplatin-induced apoptosis of renal tubular epithelial cells and protect diabetic nephropathy by suppressing epithelial-to-mesenchymal transition in db/db mice [64,65]. In addition, infection with adherent-invasive *Escherichia coli* up-regulates levels of miR-30c and miR-130a to reduce expressions of autophagy-related proteins in intestinal epithelial cells, suggesting that miR-30c is involved in autophagy [66]. Intraperitoneal (i.p.) injection of 30 μmol/kg NaHS for 48 h could protect the spinal cord by inducing autophagy via miR-30c in a rat model of spinal cord I/R injury [67], which can be attributed to the inhibitory effect of H_2S on the activity of Beclin-1 3′-untranslated region under the condition of ischemic. These results suggest that miR-30c could be a promising prognostic marker or therapeutic candidate for spinal cord I/R injury. Furthermore, many miRNAs have been shown to be involved in the modulation of autophagy by regulating the expression of autophagy-related genes or proteins [67–70]. Therefore, the roles of these miRNAs in H_2S-mediated autophagy should be further clarified.

3. The anti-autophagy effect of H_2S

An increasing number of studies suggest that many signaling pathways play important roles in the anti-autophagy effect of H_2S (Fig. 4), including scavenger receptor class A (SR-A) signaling pathway, PI3K/Serum- and glucocorticoid-responsive kinase-1 (SGK1)/glycogen synthase kinase-3β (GSK3β) signaling pathway, PI3K/AKT/mTOR signaling pathway, NF-E2-related factor 2 (Nrf2)-reactive oxygen species (ROS)-AMPK signaling pathway, AMPK/mTOR signaling pathway, and c-Jun N-terminal kinase 1 (JNK1) signaling pathway.

3.1. SR-A signaling pathway

SR-A, also called macrophage scavenger receptor, is mainly expressed on the Golgi apparatus or on the plasma membrane of macrophages [71]. SR-A plays an important role in several macrophage-associated biological processes and pathological conditions resulting from non-infectious diseases, such as adhesion, phagocytosis, and atherosclerosis [72–74]. SR-A could initiate the host innate immune response by mediating direct phagocytosis of pathogenic bacteria and recognizing diverse pathogen-associated molecular patterns [75,76]. Furthermore, SR-A activation inhibits endoplasmic reticulum (ER) stress-induced autophagy in macrophages [77]. It has been shown that H_2S can suppress ER stress which is able to induce autophagy. Thus, it is reasonable to draw a conclusion that H_2S could suppress autophagy [78]. A recent study shows that administration of 100 μg/kg NaHS (i.p. injection) after 50 min of ischemia could reduce renal I/R injury by inhibiting ER stress-induced autophagy via SR-A signaling pathway in rats [78]. Further studies are needed to determine whether H_2S could alleviate I/R injury by reducing autophagy via SR-A signaling pathway in other organs and/or tissues.

Fig. 4. A schematic illustration of the signaling pathways involved in the anti-autophagy effect of H_2S [8]. H_2S, hydrogen sulfide; Nrf2, NF-E2-related factor 2; ROS, reactive oxygen species; AMPK, adenosine monophosphate-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; Akt (PKB), protein kinase B; mTOR, mammalian target of rapamycin; SGK1, Serum- and glucocorticoid-responsive kinase-1; GSK3β, glycogen synthase kinase-3β; JNK1, c-Jun N-terminal kinase 1; SR-A, scavenger receptor class A; ER, endoplasmic reticulum.

3.2. PI3 K/SGK1/GSK3β signaling pathway

PI3 K plays a key role in regulating many cellular processes including cell growth, proliferation, survival, and motility [79]. SGK1 can be detected in a number of tissues, but their levels vary between different cell types [80]. SGK1 can be activated by PI3 K and the catalytic domain of SGK1 is similar to that of AKT and shares a variety of downstream substrates with AKT [81,82]. GSK3β, an important downstream target of both SGK1 and AKT, has been found to protect the myocardium against I/R injury by modulating mTOR and autophagy [81,83,84]. It has been reported that administration of 30 μM NaHS before hypoxia-reoxygenation (H/R) can exert a cardioprotective effect and inhibit autophagy in neonatal rat cardiomyocytes exposed to H/R partly by regulating PI3 K/SGK1/GSK3β signaling pathway, which is parallel to the PI3K/AKT signaling pathway [81]. Whether H_2S is able to reduce myocardial I/R injury by inhibiting autophagy via PI3K/SGK1/GSK3β signaling pathway should be investigated by further experiments.

3.3. PI3 K/AKT/mTOR signaling pathway

The PI3K/AKT/mTOR signaling pathway is crucial to many aspects of cell growth and survival in both physiological and pathological conditions [27,85]. The activation of this pathway leads to a profound disturbance of control of cellular function, which ultimately results in a competitive growth advantage, angiogenesis, metastatic competence, and therapy resistance [85–87]. Novel agents targeting PI3K/Akt/mTOR signaling pathway are able to improve the therapeutic effects achieved so far through higher potency and selectivity, as well as combinability with other therapeutic strategies [85]. There is increasing evidence that PI3K/AKT/mTOR pathway plays an important role in the process of autophagy. As shown in Table 2, H_2S could attenuate autophagy via the signaling pathway in several disease models. In combination with the previous finding [32], we can draw a conclusion that H_2S could exert opposite effects on autophagy through the activation/inactivation of the PI3K/AKT/mTOR signaling pathway, which may be attributed to the concentration and reaction time of H_2S and the differences among disease models. Therefore, PI3K/Akt/mTOR pathway may be a useful target for treating diseases, including I/R injury, diabetes, and hepatitis.

3.4. Nrf2-ROS-AMPK signaling pathway

Oxidative stress involves cellular or molecular damage caused by ROS, resulting from insufficient levels of antioxidants and/or antioxidant enzyme systems [92,93]. Excessive ROS can result in deoxyribonucleic acid damage, protein misfolding, organelle injury, and neuronal synaptic dysfunction [94]. In animals, the transcription factor Nrf2 is essential for the oxidative and electrophilic stress responses [95]. AMPK, a key energy sensor of cellular metabolism, plays an important role in neurodegeneration, inflammation, and oxidative stress [93]. In addition, AMPK could mediate the inactivation of GSK3β to increase nuclear accumulation of Nrf2 [96]. Excessive autophagy induced by extravagant oxidative stress contributes to diabetes-induced vascular endothelial dysfunction. For example, treatment with 100 μmol/kg NaHS (i.p. injection) every two days for 12 weeks could protect mouse arterial endothelial cells by suppressing excessive autophagy induced by oxidative stress through the Nrf2-ROS-AMPK signaling pathway [97]. The above results suggest a novel therapeutic strategy for diabetes-induced arterial endothelial injury [97].

3.5. AMPK/mTOR signaling pathway

AMPK/mTOR pathway has been widely studied since it is sensitive to nutrition and energy status [98]. mTOR could integrate and coordinate a series of sensory inputs from upstream pathways to regulate the autophagic process [99,100]. Once activated, mTOR inhibits autophagy via phosphorylation of the Atg proteins [101]. AMPK activation results in autophagy through negative regulation of mTOR, and many other factors involved in the autophagic process could regulate autophagy through AMPK/mTOR signaling [101–104]. A recent study indicates that intragastric administration of NaHS solution at a dose of 8 μmol/kg/day for 4 months could reduce smoking-induced autophagic cell death via regulation of AMPK/mTOR signaling pathway in rats

Table 2
H_2S attenuates autophagy via the PI3K/AKT/mTOR signaling pathway.

Experimental models	Effects	Proposed mechanisms	Refs.
Diabetes (Rat)	Treatment with NaHS (100 μmol/kg) for 8 weeks protects against diabetes-induced myocardial fibrosis	Attenuation of autophagy via the upregulation of the PI3K/AKT1 signaling pathway	[88]
Myocardial H/R injury (Rat)	Treatment with NaHS (30 μM, 30 min before H/R) attenuates myocardial H/R Injury	Inhibition of autophagy through the activation of the Akt/mTOR pathway	[26]
Spinal cord ischemic reperfusion (SCIR) injury (Rat)	Treatment with NaHS (5.6 mg/kg, 1 h before the onset of spinal cord I/R) can exert a neuroprotective role in SCIR injury	Inhibition of autophagic cell death by reducing oxidative stress in SCIR injury via the Akt/mTOR pathway	[89]
Concanavalin A (Con A)-induced hepatitis (Mouse)	Treatment with NaHS (14 μmol/kg, 1 h prior to Con A injection) attenuates Con A-induced acute hepatitis	Inhibition of apoptosis and autophagy partly through activation of the PI3K/AKT1 signaling pathway	[90]
Alcoholic cardiomyopathy (Mouse)	Treatment with NaHS (50 μmol/kg) for 12 weeks alleviates myocardial fibrosis in mice with alcoholic cardiomyopathy	Downregulation of autophagy through the activation of the PI3K/AKT1 pathway	[91]

[105]. Whether H_2S-releasing donors are able to alleviate cigarette smoking-induced left ventricular systolic dysfunction in other animal models need to be further investigated.

3.6. JNK1 signaling pathway

In response to changes in the environment, cells often undergo phenotypic transitions through the mitogen-activated protein kinase (MAPK) signaling pathway [106]. In the light of the external signal present, the temporal and spatial properties of MAPK regulation may prompt cells to grow, proliferate, differentiate, or adapt to different types of stresses [107]. Extracellular signal-regulated protein kinase 1/2 (ERK1/2), JNK, and p38 are three major components of MAPKs that play important roles in inflammation, apoptosis, and autophagy [108–110]. Administration of NaHS (0.2 mg/kg injected over 10 s followed with infusion 2 mg/kg/h) could offer biochemical myocardial protection via the activation of ERK1/2 and attenuation of caspase-independent apoptosis and autophagy in both cardioplegia and cardiopulmonary bypass [111]. Another study indicates that i.p. injection of 1 mL of NaHS solution (28 μmol/kg) 30 min before I/R attenuates hepatic I/R injury partly by reducing apoptosis and autophagy through inhibiting JNK1 signaling in mice [112]. Considering JNK1 is one of the major components of MAPKs, further studies are needed to determine whether H_2S could decrease autophagy through the MAPK signaling pathway.

4. Conclusion

H_2S is now recognized as the third endogenous gasotransmitter and can be endogenously generated through four enzymatic pathways in mammals. Whether H_2S could be generated via another pathway should be further studied and confirmed. H_2S plays important roles in a wide range of physiological and pathological conditions. However, recent studies indicate that endogenously produced and/or exogenously administered H_2S could exhibit two obviously opposite effects on autophagy in a number of disease models, which may be attributed to the concentration, time frame, and reaction time of H_2S, as well as the differences between disease stages or models. Autophagy is an evolutionarily conserved process which degrades dysfunctional organelles and damaged proteins to promote cell survival under stress conditions [113,114]. However, beyond a certain range, it eventually results in cell death, with the excessive accumulation of autophagosomes [115]. Therefore, the diverse effects of H_2S on autuphagy may be partly dependent on the different levels of basal autophagy in different types of cells. Further investigations are needed to detect the effect of H_2S on autophagy in other disease models, which may contribute to the elucidation of the precise mechanism of H_2S in autophagy and the development of novel autophagy-targeted drugs. Future studies need to define the roles of endogenous H_2S produced by CSE, CBS, and 3-MST in regulating autophagy in specific mammalian tissues and cell types. Furthermore, recent studies mainly focus on the effects of NaHS on autophagy, the roles and mechanisms of novel H_2S donors in autophagy should be further investigated.

Recent studies indicate that a number of signaling pathways are involved in the pro-autophagy effect of H_2S, such as PI3K/Akt/mTOR, AMPK/mTOR, LKB1/STRAD/MO25, and miR-30c signaling pathways. On the other hand, there are many signaling pathways that play important roles in the anti-autophagy effect of H_2S, including SR-A, PI3K/SGK1/GSK3β, PI3K/AKT/mTOR, Nrf2-ROS-AMPK, AMPK/mTOR, and JNK1 signaling pathways. These signaling pathways may be promising targets for treating a number of diseases, including I/R injury, acute pancreatitis, diabetes, and hepatitis. Further studies are needed to determine whether these signaling pathways contribute to H_2S-mediated autophagy in other disease models. In addition, recent studies have demonstrated that H_2S could attenuate cerebral I/R injury by inhibiting autophagy in both rats and mice [116,117]. However, more efforts should be paid to clarify the underling mechanisms. Furthermore, apart from the existing signaling pathways, novel signaling pathways should be clarified in H_2S-mediated autophagy in various disease models. Moreover, novel H_2S-releasing donors should be designed and identified in order to increase the therapeutic effects by mediating autophagy in human diseases.

In conclusion, with a deeper understanding of the precise signaling pathways behind the role of H_2S in the process of autophagy, treatment with a proper dose of H_2S or its donors for an appropriate period of time could be promising strategies for further preclinical and clinical research.

Conflicts of interest

The authors declare that they have no conflicts of interest related to this work.

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