Hydrogen Sulfide Regulating Myocardial Structure and Function by Targeting Cardiomyocyte Autophagy

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Abstract

Objective: Hydrogen sulfide (H_2S), a gaseous signal molecule, plays a crucial role in many pathophysiologic processes in the cardiovascular system. Autophagy has been shown to participate in the occurrence of many cardiac diseases. Increasing evidences indicated that H_2S regulates myocardial structure and function in association with the altered autophagy and plays a "switcher" role in the autophagy of myocardial diseases. The aim of this review was to summarize these insights and provide the experimental evidence that H_2S targets cardiomyocyte autophagy to regulate cardiovascular function.

Data Sources: This review was based on data in articles published in the PubMed databases up to October 30, 2017, with the following keywords: "hydrogen sulfide," "autophagy," and "cardiovascular diseases."

Study Selection: Original articles and critical reviews on H_2S and autophagy were selected for this review.

Results: When autophagy plays an adaptive role in the pathogenesis of diseases, H_2S restores autophagy; otherwise, when autophagy plays a detrimental role, H_2S downregulates autophagy to exert a cardioprotective function. For example, H_2S has beneficial effects by regulating autophagy in myocardial ischemia/reperfusion and plays a protective role by inhibiting autophagy during the operation of cardioplegia and cardiopulmonary bypass. H_2S postpones cardiac aging associated with the upregulation of autophagy but improves the left ventricular function of smoking rats by lowering autophagy.

Conclusions: H_2S exerts cardiovascular protection by regulating autophagy. Cardiovascular autophagy would likely become a potential target of H_2S therapy for cardiovascular diseases.

Key words: Autophagy; Cardioprotective Function; Cardiovascular System; Hydrogen Sulfide

INTRODUCTION

Autophagy is a complex intracellular process that delivers damaged or unnecessary proteins and organelles to lysosomes for degradation.[1] Autophagy plays a key beneficial role in cell survival.[2] The up- or down-regulation of autophagy can lead to cell death, which plays a role in the occurrence and development of cardiovascular disease.[3] The regulation of autophagy may become a potential target for the prevention and control of cardiovascular disease. However, the factors responsible for regulating autophagy and the strategy to control autophagy remain unclear.[3]

Multiple studies have shown that hydrogen sulfide (H_2S) can regulate autophagy which further affects the progress of cardiovascular diseases.[4] Therefore, we have reviewed

and summarized the role of H_2S in the regulation of cardiovascular autophagy and its clinical significance using existing literature.

AUTOPHAGY IN MYOCARDIAL DISEASES

Cardiomyocyte autophagy was first discovered in the 1970s.[4] Subsequently, an increasing number of scientists

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have focused on studying how autophagy regulates cardiovascular homeostasis and disease.[5] However, it was not until the year 2000 that we witnessed great growth in the investigation of autophagy in the cardiovascular system.[3]

Autophagy is a catabolic process that is evolutionarily conserved and strictly regulated. It is primarily performed in the body to deliver long-lived proteins and organelles for degradation to the lysosome.[6,7] Up to now, three distinct forms of autophagy have been identified: chaperone-mediated autophagy,[8] microautophagy,[9] and macroautophagy.[6,7] Autophagy is a very complicated process involving many molecules, and the typical molecules include Beclin-1 and protein 1 light chain 3 (LC3-II/I). There are four steps in the process of autophagy: (1) phagophore formation, the initial process; (2) formation of a double-membrane autophagosome, the landmark step; (3) fusion of autophagosomes with lysosomes and the formation of autolysosomes; and (4) degradation of autophagy contents, including long-lived proteins and dysfunctional organelles, with subsequent recruitment of the digested contents to the cytoplasm where they can be reused for anabolic reactions or the synthesis of other structures.[10]

So far, multiple studies have demonstrated the existence of autophagy in cardiovascular tissues[2,10] and that autophagy levels rise or fall under different conditions. In fact, autophagy remains at a low basal level under normal conditions and plays a crucial role in maintaining homeostasis of the cardiovascular system.[11,12] Under internal or external stimuli from certain cells, such as starvation, heart failure, chronic ischemia and cardiomyopathy, autophagy is upregulated.[13-15] Nevertheless, autophagy exerts both protective and harmful effects. In most but not all cases, autophagy is reflective of a survival mechanism. For example, Loos et al.[16] found that autophagy delays the onset of both apoptotic and necrotic cell death during mild ischemic stress and plays a vital role in survival. In 2013, Dai et al.[17] showed that autophagy protects against vascular smooth muscle cell (VSMC) calcification induced by phosphate through promoting apoptosis and suppressing matrix vesicle release. However, under other circumstances, it may play a deleterious role. In 2011, Mellor et al.[18] first found that autophagy contributes to cardiac lesions together with the inhibition of cell survival signaling and the excessive production of reactive oxygen species in fructose-fed animals. Li et al.[19] demonstrated that human c-ski proto-oncogene product (c-Ski) protected VSMCs against harsh stress including oxidized low-density lipoprotein and platelet-derived growth factor by inhibiting autophagy.

Although autophagy exists extensively in the cardiovascular system and plays a vital role in cardiovascular function, the regulatory mechanisms for autophagy are not clear. However, a large aggregation of research attests to the fact that H2S can inhibit or promote autophagy in different cases, thus playing cardiovascular protective roles.

Generation of Endogenous Hydrogen Sulfide and Its Function in the Cardiovascular System

For many years, H2S has been solely viewed as a poisonous gas with an unpleasant smell. Growing evidence revealed that H2S can be produced endogenously in multiple organ systems in the body of mammals, including humans, fish, and plants.[20-25] Endogenous H2S is generated by various enzymatic and nonenzymatic steps. In mammals, H2S is produced mainly in enzymatic reactions in a process involving sulfur-containing amino acid metabolites.[26] Scientists have confirmed that three enzymes involved in the production of H2S, namely, cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and 3-mercapto sulfurtransferase (3-MST). CSE and CBS, two vitamin B6-dependent enzymes expressed in the cytosol, are responsible for endogenous production in most mammalian cells, primarily of the substrate L-cysteine.[27-30] The 3-MST, a zinc-dependent enzyme produced both in mitochondria and in the cytosol, catalyzes the reaction of α-ketoglutarate to H2S through metabolic interactions with cysteine aminotransferase.[31] Different enzymes are involved in the production of H2S in different tissues. H2S is predominantly synthetized in the cardiovascular system, and its concentration varies from one tissue to another (e.g., pulmonary artery > aortic > mesenteric artery),[32] whereas CBS is present in the brain and the nervous system,[27,33,34] and 3-MST is found mainly in the brain and red blood cells.[35]

H2S is widely involved in the pathophysiological processes of cardiovascular systems. Our laboratory has proven that endogenous H2S in the rat could maintain the basal blood pressure balance, attenuate elevated blood pressure, and lessen vascular structural remodeling in spontaneously hypertensive rats.[36] Meanwhile, Geng et al.[37] found that H2S could improve left heart function and reduce the mortality rate in rats with myocardial injury induced by isoproterenol. In addition, H2S has therapeutic potential for diseases such as ischemia/reperfusion (I/R) injury in the heart,[38] and ameliorates ischemia-induced heart failure in mice.[39]

Hydrogen Sulfide Affects Autophagy in Different Myocardial Diseases

H2S can regulate autophagy in many diseases and induce or inhibit autophagy flux in different cells or diseases.[40-42] For example, H2S lowers proliferation and induces protective autophagy in colon epithelial cells.[40] However, exogenous H2S attenuates cerebral I/R injury by inhibiting autophagy in mice.[41] In the cardiovascular system, H2S also exerts a cardioprotective effect by modulating autophagy. In some studies, it was reported that in the animal model of cardiomyopathy, H2S could attenuate myocardial autophagy and ameliorate myocardial fibrosis by downregulating autophagy.[43,44] However, other research teams reported that H2S could protect myocardiocytes by promoting autophagy in a type 2 diabetes model.[45,46] Thus, how H2S

exerts its protective effects on cardiomyocytes through autophagy merits further studies. We reviewed various studies investigating the regulation of autophagy by H_2S in cardiovascular diseases to shed new light on the mechanisms for the cardioprotective role of H_2S.

HYDROGEN SULFIDE EXERTS BENEFICIAL EFFECTS BY REGULATING AUTOPHAGY IN MYOCARDIAL ISCHEMIA-REPERFUSION

Numerous studies have focused on the investigation of autophagy in I/R injury, where autophagy plays a paradoxical role.[2] During ischemia, the deprivation of nutrients leads to the activation of autophagy through AMP-activated protein kinase (AMPK), and autophagy promotes survival during ischemia.[42] However, reperfusion induces a different response from ischemia. Research suggests that myocardial autophagy can play either an adaptive or a detrimental role in the reperfusion and that beclin activation but not AMPK/mammalian target of rapamycin (mTOR) is involved in the course.[42] Indeed, it is not clear whether the changes in autophagy induced by reperfusion play beneficial or detrimental roles in the myocardium. Thus, the regulating effect of H_2S on autophagy in myocardial cells exposed to I/R also exhibits discrepancies. Therefore, H_2S seems to switch autophagy from a beneficial to a detrimental role in I/R.[2]

Osipov et al.[47] investigated the effect of H_2S on a myocardial I/R model in pigs. In that study, pigs were subjected to obstruction of the mid left anterior descending coronary artery for 60 min followed by reperfusion for 120 min. These pigs received either placebo (control) or H_2S as a bolus (bolus group, 0.2 mg/kg over 10 s at the beginning of reperfusion) or as an infusion (infusion group, 2 mg·kg^{-1}·h^{-1} initiated at the onset of ischemia and continued into the reperfusion period). These pigs were randomly divided into three groups. Animals in the control group received a placebo, while those in the bolus group received H_2S as a bolus (0.2 mg/kg over 10 s at the beginning of reperfusion), and those in the infusion group received an H_2S infusion as 2 mg·kg^{-1}·h^{-1} initiated at the onset of ischemia and continued into the reperfusion period. The researchers found that in the H_2S infusion group, the myocardial infarct size was significantly decreased by 64% and that the coronary microvascular reactivity and regional LV function improved during the acute I/R period. In addition, compared with the control and bolus group, the expression of mTOR was low, whereas the ratio of phospho-mTOR to the total mTOR was high in the infusion H_2S group.[47] Phospho-mTOR, the activated form of mTOR, played a key role in mTOR function control.[48] The authors concluded that the continuous infusion of H_2S, which was initiated at the onset of ischemia and continued into the reperfusion period, distinctly exerted a protective effect in myocardial I/R injury. In addition, these protective roles of H_2S are associated with ameliorating coronary microvascular relaxation, improving expression of cell survival protein, and decreasing apoptosis and autophagy.[47] Moreover, Decker and Wildenthal[49] subjected rabbit hearts to 40 or 60 min of ischemia and subsequent reperfusion, respectively, and observed that the former condition caused the activation of autophagy whereas the latter blocked the autophagy pathway. In other words, 60 min of ischemia inhibited autophagy. That is, H_2S suppressed autophagy during the reperfusion phase of the experiment.

In addition, Loos et al.[16] used H9c-2 rat heart myoblasts to study the functional role of autophagy in myocardial I/R. They observed that autophagy and apoptosis were upregulated during mild ischemia, and despite the increasing number of apoptotic and necrotic cell deaths, autophagy was not induced under moderate or severe ischemia. Collectively, they found that only in mild injury autophagy was upregulated and provided cardiac cell protection.[17] Studies reported that the expression of Beclin-1 is markedly upregulated during the reperfusion phase.[43,50] Osipov et al.[47] observed that in a bolus group receiving H_2S, Beclin-1 was weakly expressed. Furthermore, a study by Matsui et al.[42] showed that low levels of autophagy during reperfusion reduced apoptosis and narrowed the infarct size. The authors suggested that autophagy in I/R plays opposite roles that autophagy is beneficial during ischemia but is detrimental during reperfusion. These findings helped us reach a conclusion parallel to that in the experiment by Decker and Wildenthal,[49] who demonstrated that autophagy was reduced during 60 min of ischemia and that H_2S reduced the level of autophagy during the reperfusion phase. However, this requires further confirmation by experiments.

Recently, Xie et al.[51] reported that using 5-(4-methoxyphenyl)-3H-1,2-dithiole-3-thione (ADT), a slow-releasing H_2S donor, could activate AMPK and restore an I/R-impaired autophagy flux to play a protective role in myocardial I/R injury. After ischemia, the ADT was administered, and it activated AMPK to protect against myocardial injury during I/R. Moreover, the cardioprotective mechanisms for H_2S donor consisted of the activation of AMPK and subsequent restoration of the impaired autophagy flux during myocardial I/R injury.[51] However, Jiang et al.[52] found that H_2S could play a significantly protective role in myocardial IR injury by down-regulating the autophagy pathway. The mRNA levels of autophagy-related genes Atg5, Beclin-1, and Atg9 and the protein levels of Beclin-1 and LC3-II/I as the widely used markers of autophagy were significantly decreased when H_2S was administered after ischemia. In addition, in neonatal rat cardiomyocytes exposed to hypoxic/reoxygenation injury, H_2S plays cardioprotective roles. The mechanisms are partly related to the anti-autophagic action of H_2S through the PI3K/SGK1/GSK3β signaling pathway.[52]

To the best of our knowledge, age-related changes in autophagy in the heart are recognized.[53] H_2S regulation of autophagy in the cardiovascular system was also influenced by age. In neonatal cardiomyocytes, Xiao et al.[54] also reported that H_2S played a myocardial protective role in I/R injury by inhibiting autophagy through mTOR activation. However, in aging hearts and cardiomyocytes,

Chen et al.[55] found that H$_2$S restored cardioprotection from postconditioning by upregulation of autophagy through activation of AMPK/mTOR pathway.

Based on the above studies, we hypothesized that H$_2$S performs an autophagy switcher role in I/R. When autophagy plays an adaptive role in the ischemia, H$_2$S restores the autophagy flux by activating AMPK; otherwise, when autophagy plays a detrimental role in the reperfusion, H$_2$S down-regulates autophagy to influence radioprotection. If the hypothesis is borne out by further studies, it will have interesting relevance for the mechanisms underlying the cardioprotective effects of H$_2$S.

HYDROGEN SULFIDE PLAYS A PROTECTIVE ROLE BY INHIBITING AUTOPHAGY IN THE OPERATION OF QUADRIPLEGIA AND CARDIOPULMONARY BYPASS

Cardiopulmonary bypass (CPB) including cardioplegia (CP) is necessary to allow for safe operation during cardiac surgery on a nonbeating heart when coronary artery blood flow is blocked and to reduce myocardial injury caused by ischemia. However, CP/CPB can cause myocardial apoptosis, coronary microvascular dysfunction and inflammation, leading to myocardial damage.[56] Researchers continue to explore solutions to mitigate its side effects. Based on the cardiovascular protection of H$_2$S in various cases, Osipov et al.[57] tested the hypothesis that exogenous H$_2$S reduced heart injury in a porcine model of CP/CPB. In this study, male Yorkshire pigs (30–35 kg) were exposed to 1 h of CP/CPB and 2 h of reperfusion injury, and the pigs were then divided into 3 groups. The pigs in the control group were given saline vehicle as a placebo, while those in the infusion group were administered an infusion of NaHS alone. Those in the bolus/infusion group were given a bolus followed by an infusion of NaHS. Similar to the previous assumptions, H$_2$S administration promoted the expression of pro-survival proteins such as heme oxygenase-1, phosphorylated heat shock protein 27, and phosphorylation of Erk 1/2 but reduced the expression levels of B-cell lymphoma 2/Bnip-3 (adenovirus E1B 19 kDa-interacting protein). Meanwhile, H$_2$S was beneficial for coronary microvascular reactivity to adenosine diphosphate. It was also observed that the expression of the ratio of microtubule-associated LC3-II/I, an important marker of autophagy in the infusion group, was lower than that of other groups. On the basis of the above indicators, the authors concluded that H$_2$S possessed cardioprotective effects in the setting of CP/CPB and this advantage was attributed to the attenuation of caspase-independent apoptosis and autophagy.[57]

HYDROGEN SULFIDE POSTPONES CARDIAC AGING ASSOCIATED WITH THE UPREGULATION OF AUTOPHAGY

Aging is associated with a progressive decline in many organs, including the heart. Cardiac aging results in the left ventricular (LV) fibrosis and diastolic dysfunction and predisposition to heart failure.[58] Although the intimate mechanisms involved in cardiac senescence are not fully understood, it is undisputed that mitochondrial oxidative stress and mitochondrial dysfunction are closely related to the age-related cardiovascular pathologies.[59] Notably, emerging evidence has revealed that mitophagy is currently the only determined mechanism for insulating and degrading the impaired mitochondria.[60] Alternatively, an age-related impairment of autophagy has been reported in various mammalian tissues including the heart,[12,61] which further indicated the intrinsic relationships between myocardial aging and autophagy.[62]

In 2013, Talaei et al.[63] found that the expression levels of CBS, CSE, and sirtuin-1 (SIRT-1), which maintain the proliferative capacity by overcoming senescence, were strongly down-regulated in a type of prematurely aging cell whereas the activation of mTOR was promoted, compared with the normal controls. Nevertheless, NaHS treatment improved this situation through hindering mTOR activation and increasing the expression of SIRT-1 and the LC3-II/LC3-I ratio, which determined the autophagy levels and thus prevented premature aging. Analogously, Luo et al.[64] showed that SIRT1 distinctly protected against cardiovascular aging by promoting autophagy and that the mechanisms for inducing autophagy involved inhibiting the IGF-Akt-mTOR signaling pathway. Luo et al.[64] concluded that H$_2$S augmented SIRT1 expression, then repressed mTOR, directly inhibited mTOR, activated autophagy, and ultimately protected against cardiovascular aging. In short, H$_2$S exerts beneficial effects on cardiovascular aging by enhancing autophagy. In fact, impaired autophagy is closely related to the aging of other organs, such as retina.[65]

HYDROGEN SULFIDE AMELIORATES THE LEFT VENTRICULAR FUNCTION IN SMOKING RATS BY LOWERING AUTOPHAGY

It has been confirmed that chronic cigarette smoke exposure exerts effects on cardiac structure and function.[66] Recently, Zhou et al.[67] reported that H$_2$S decreases the autophagy and apoptosis of cardiac cells to ameliorate LV systolic function. Their results demonstrated that LV remodeling and dysfunction significantly improved and that the apoptotic cardiomyocytes were significantly decreased, accompanied by the decreased expression of apoptosis regulatory proteins in the cigarette-smoking rats receiving NaHS treatment compared with those without NaHS treatment. In addition, the expression of autophagy-related proteins and autophagosomes was significantly higher in the cigarette-smoking rats than in the control group, whereas it was significantly reduced in the cigarette-smoking rats receiving NaHS treatment compared with those not administered NaHS. Thus, the authors concluded that H$_2$S down-regulated the apoptosis and autophagy of cardiomyocytes to play a protective role in the LV systolic function of cigarette-smoking rats.[67] Although an increasing number of publications are reporting that autophagy plays a

role in the pathological mechanisms responsible for chronic heart failure,[68] there is also a large body of evidence suggesting that H_2S lessens autophagy-related indicators; however, it is difficult to fully demonstrate whether the cardioprotective function of H_2S is due to inhibition of autophagy.[64]

CONCLUSION

Considerable published evidences showed that H_2S exerts cardiovascular protection by blocking or enhancing autophagy. However, many unanswered questions remain. Right now, it is difficult to fully demonstrate a causal relationship between the cardioprotective effect of H_2S and its inhibition or regulation of autophagy. However, with the increasing accumulation of knowledge regarding the regulation of autophagy and the role of H_2S in the cardiovascular system, cardiovascular autophagy will likely become a potential target of H_2S therapy for cardiovascular diseases.

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There are no conflicts of interest.

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硫化氢通过心肌细胞自噬途径参与心脏结构和功能的调节

摘要

目的： 硫化氢，一种新型气体信号分子，在心血管系统多种病理生理过程中发挥重要的调节作用。而心肌细胞的自噬参与多种心血管疾病的发生发展过程。越来越多的研究发现硫化氢可通过调节心肌细胞的自噬作用影响心脏的结构和功能。本文即是对硫化氢通过心肌细胞自噬途径调节心脏结构和功能的相关研究展开综述。

数据收集： 本文收集了直至2017年10月30日在PubMed数据库内的关于硫化氢通过自噬参与心血管系统调节的文章。所有关键词是"硫化氢"、"自噬"及"心血管疾病"。

论文选取标准： 所有在心血管系统中研究关于硫化氢与自噬的论著及重要的综述均包含在本文研究范围内。

结果： 当自噬在疾病发展过程中发挥代偿性保护作用时，硫化氢可通过促进自噬作用发挥对心血管系统的保护作用，而当自噬在疾病发生发展过程中发挥不利作用时，硫化氢又可通过下调心肌细胞的自噬作用来发挥对心血管系统的保护作用。硫化氢在心血管系统中对自噬具有类似"调节器"的作用。比如，在心肌的缺血再灌注损伤中，硫化氢可通过上调心肌的自噬作用发挥其心肌保护作用，而在心脏停搏与体外循环的手术中，心肌细胞的自噬对心肌保护不利时，硫化氢又可通过抑制心肌细胞的自噬发挥其心肌保护作用。同样，硫化氢可通过上调心肌细胞的自噬来延缓心肌细胞的老化，而在吸烟的大鼠模型中，硫化氢可通过减弱心肌细胞的自噬来保护由于吸烟导致的左心室功能的受损。

结论： 调节心肌细胞的自噬作用可能是硫化氢的心血管系统保护作用的机制之一。