Myocardial Protective Effect of Gas Signal Molecule Hydrogen Sulfide on Cardiovascular Disease

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ABSTRACT

Cardiovascular diseases increase continually in the worldwide scale, and its specific pathogenesis has not been completely clear. The gas signal molecule hydrogen sulfide (H$_2$S) is a new type of neuroactive substance, which plays many biological roles in many systems such as cardiovascular system. In recent years, a lot of research has confirmed H$_2$S has myocardial protective effect on cardiovascular diseases such as atherosclerosis, ischemia-reperfusion injury, hypertension and heart failure. This paper reviews the research status of myocardial protective effect of H$_2$S on cardiovascular diseases.

1. The Research Background

With the continuous progress of social development level and the aging process of population structure in China, the continuous increase of cardiovascular patients received in clinic, which has seriously affected people’s health[1]. In the past decade, scholars at home and abroad have done a lot of researches on the prevention and treatment of cardiovascular disease, but still have not found an effective cure[2]. In 2014 Xu et al[3] studies indicate that the behavior of hydrogen sulfide (H$_2$S) is similar to nitric oxide (NO) and carbon monoxide (CO), and may exert myocardial protective effects by inhibiting mitochondrial pathways, resisting Ca$^{2+}$ overload and antioxidant stress. This paper will summarize and analyze the latest research progress of H$_2$S in myocardial protection and therapeutic potential in cardiovascular system diseases such as ischemia-reperfusion injury, atherosclerosis, hypertension and heart failure of recent years, the aim is to provide a new idea for the clinical prevention and treatment of cardiovascular diseases such as ischemia-reperfusion injury.

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2. Generation and Metabolism of H$_2$S

The production of H$_2$S in mammals has two pathways: non-enzyme catalysis and enzyme catalysis. H$_2$S in the non-enzyme pathway is mainly produced by elemental sulfur and sulfur-containing compounds, only a small part of H$_2$S is produced by the non-enzyme catalytic pathway, and most of H$_2$S is produced by the enzyme catalytic pathway. It has been found that the production of endogenous H$_2$S is regulated by the following five enzymes: D-amino acid oxidase (DAO), cysteine-lyase (CSE), cysteine-synthase (CBS), cysteine transaminase (CAT), and 3-mercaptopuruvate sultransferase (3-MST)[5]. For example, DAO is mainly distributed in the kidney and cerebrum, CBS is mainly distributed in the central nervous system, CAT and 3-MST can synthesize H$_2$S in the brain and vascular endothelium, and CSE is the most critical enzyme in the sulfur transfer pathway of the human cardiovascular system[6]. L-cysteine is the main catalytic substrate for CSE, CBS and CAT, while D-cysteine is the substrate for DAO and 3-MST[7]. H$_2$S generated in the body is mainly characterized in two forms: 1/3 is in the form of H$_2$S, and 2/3 is in the form of Sodium hydrosulfide (NaHS), H$_2$S and NaHS can be transformed into each other and form a dynamic balance in vivo[8](H$_2$S: NaHS=1:2). The endogenous H$_2$S is rapidly oxidized to thiosulphates and sulfates in the mitochondria of cells catalyzed by a variety of enzymes and detoxified, and finally discharged through the kidneys, intestines and lungs[9].

3. Effects of H$_2$S on Cardiovascular Disease

Endogenous H$_2$S level is mainly regulated by H$_2$S generating enzyme. When the expression or activity of the generating enzyme is down-regulated, H$_2$S level will be significantly reduced, leading to cardiovascular disease. Gao et al.[10] found in their study that compared with normal subjects, Plasma H$_2$S level was significantly reduced in patients with coronary atherosclerosis. Hong Kong et al. conducted a study on 110 patients with coronary heart disease using sensitive sulfur electrode method to determine the plasma H$_2$S content and found that the plasma H$_2$S level in patients with acute myocardial infarction and unstable angina was lower than that in patients with stable angina[11]. Salloum et al.[12]. Found that endogenous H$_2$S can not only reduce myocardial ischemia-reperfusion injury, but also regulate blood pressure, fight atherosclerosis, promote vasodilation and regulate negative myocardial strength. The myocardial protective effect of endogenous H$_2$S on cardiovascular diseases has been confirmed, and the myocardial protective effect of exogenous H$_2$S on cardiovascular diseases has been gradually confirmed. Supplementation of exogenous H$_2$S can also reduce myocardial injury, improve heart failure and improve cardiac function.

3.1 H$_2$S and Ischemia-Reperfusion Injury

Myocardial ischemia is mainly refers to the blood perfusion of heart is reduced caused by Atherosclerosis (AS), leading to reduced oxygen supply to the heart, circulatory failure, or even sudden death, reperfusion is necessary to improve myocardial ischemia, but the injurious changes caused in the ischemic period are more serious after recanalization, irreversible myocardial damage, serious arrhythmia and even lead to sudden death. Through comparative analysis of 100 patients with acute myocardial infarction and 100 patients with normal coronary angiography, He Bosheng et al.[13] found that H$_2$S content could determine the scope and clinical efficacy of myocardial infarction, and confirmed that H$_2$S has a certain correlation with myocardial ischemia reperfusion injury. When myocardial ischemia occurs, H$_2$S mediated chemical modification of cardiac protein is significantly increased, thereby rapidly activating protective pathways, increasing coronary microvascular reactivity, improving cardiac function, and ultimately reducing the damage caused by myocardial ischemia to the body[14]. In addition, some scholars have pointed out that pretreatment with H$_2$S donor (NaHS) before ischemia also has a certain myocardial protection effect. Studies on rat myocardial ischemia model indicate that animals with reduced CSE activity and significantly reduced endogenous H$_2$S could increase myocardial perfusion, improve arrhythmia, and thus reduce myocardial injury after artificial NaHS pretreatment[15]. The following is a summary of several major mechanisms by which H$_2$S exerts myocardial protection.

3.1.1 Mechanism 1: Anti-apoptosis

Numerous studies have shown that H$_2$S plays a crucial role in its resistance to apoptosis by inhibiting mitochondrial pathways and endoplasmic reticulum pathways. Mitochondrial pathway is the endogenous apoptosis pathway, in which the anti-apoptotic protein Bcl-2 gene and the pro-apoptotic protein Bax gene can change the mitochondrial membrane integrity, and their relative levels determine the fate of cells and are key factors affecting the survival of myocardial cells[16]. The expression of Bcl-2 gene in mitochondrial outer membrane can inhibit the transport of cytochrome C to cytoplasm and thus resist apoptosis. After activation, Bax gene is inserted the mitochondrial outer membrane through allosteric translocation, thus destroying the integrity of the membrane, and resisting destruction of the inner mitochondrial membrane resulting in cytochrome C outflow and activation of caspase. In our study, we found that after NaHS pretreatment, myocardial ischemia-reperfusion injury was significantly reduced, and the expression of Bcl-2 gene was increased. In addition, the expression of Bax gene was reduced, which is consistent with the results of other studies[17]. This further confirmed that NaHS treatment can significantly reduce ischemia-reperfusion injury of myocardial, and its mechanism may be related to anti-apoptosis.

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anti-apoptotic proteins, thus promoting cell apoptosis. H$_2$S up-regulated the expression of anti-apoptotic protein Bel-2 and decreased the expression of pro-apoptotic protein Bax, finally achieving the purpose of anti-apoptosis and protecting cardiomyocytes\textsuperscript{173}. Citi et al. found that H$_2$S inhibited apoptosis by down-regulating mRNA and protein expression levels of transcription factor homologous protein, an important molecule of unfolded protein, and glucose-regulating protein 78 during myocardial ischemia and reperfusion\textsuperscript{189}.

3.1.2 Mechanism 2: Antioxidant Stress

During ischemia-reperfusion, the increase of free radicals, reactive oxygen species (ROS) and Reactive nitrogen species (RNS) in the body leads to lipid peroxidation of biofilms, imbalance of oxidation system and antioxidant system, DNA damage, and finally myocardial cell damage\textsuperscript{190}. Al-Magableh et al. have shown that H$_2$S can reduce ROS and protect vascular endothelium under acute stress by decomposing single electron chemicals such as HS\textsuperscript{191}. Zhang et al\textsuperscript{219} treated the rats with hydrogen peroxide (H$_2$O$_2$), an activated oxygen donor, to simulate acute ischemia-reperfusion injury, the pretreatment of H$_2$S donor before H$_2$O$_2$ treatment revealed that H$_2$S donor could reduce oxidative stress, thereby protecting myocardial cells.

3.1.3 Mechanism 3: Anti-Ca$^{2+}$ Overload

During ischemia-reperfusion, a large amount of Ca$^{2+}$ aggregation can change the permeability of mitochondrial membrane by activating the phospholipase on the mitochondrial membrane, and finally cause myocardial damage. Numerous studies have demonstrated that H$_2$S protects cardiomyocytes against Ca$^{2+}$ overload, thereby reducing the incidence of cardiovascular disease. Studies have found that H$_2$S can promote the opening of ATP-sensitive potassium channels and accelerate the uptake of Ca$^{2+}$ in the sarcoplasmic reticulum. H$_2$S can also inhibit Ca$^{2+}$ overload and avoid excessive contraction of cardiomyocytes by inhibiting the opening of L-type Ca$^{2+}$ channels\textsuperscript{125}. In addition, H$_2$S can enhance the activity of Ca$^{2+}$-ATPase in the sarcoplasmic reticulum by activating protein kinase C (PKC) in myocardial tissue, accelerate Ca$^{2+}$ exchanger-mediated ion exchange, inhibit Ca$^{2+}$ overload, and thus reduce ischemia-reperfusion induced cardiac infarction. After slow injection of H$_2$S donor into myocardial ischemia rat models, Ca$^{2+}$ overload can be inhibited, thus reducing myocardial ischemia range and promoting cardiac function recovery, resulting in significant myocardial protective effects\textsuperscript{235}.

3.2 H$_2$S and Atherosclerosis

The role of H$_2$S in atherosclerosis changes cannot be ignored, such as Wang treatment with NaHS apolipoprotein E knock out (apoE -/-) mice, the study found that H$_2$S can inhibit expression of the aortic intercellular adhesion molecule -1 (ICAM 1), ICAM -1 plays an important role in the formation and development of thrombosis and AS, the direct relationship between H$_2$S and AS lesions was demonstrated for the first time\textsuperscript{174}. A large number of studies have shown that H$_2$S has various vascular protective effects against AS diseases, including regulating blood lipid content, promoting endothelial cell proliferation and migration, reducing foam cell formation, inhibiting platelet aggregation, and inhibiting the expression of aortic chemokine receptor 1 antibody (CX3CR1) and chemokine CX3CL1. Zhao et al. demonstrated that H$_2$S can inhibit the production of foam cells through the CATP/ERK1/2 pathway of human monocyte derived macrophages\textsuperscript{225}. After NaHS treatment, intracellular lipid accumulation was reduced, indicating that H$_2$S had a certain effect on inhibiting the AS lesions. Du et al\textsuperscript{260} found that H$_2$S reduces macrophage inflammation induced by ox-LDL by inhibiting the phosphorylation of nuclear factor Bp65, thereby reducing the harmful effects of lipoprotein in the development of atherosclerosis.

3.3 H$_2$S and High Blood Pressure

Collagen fibers have strong toughness and low elasticity. If the amount of collagen in the heart's blood vessels increases, narrow blood vessels, high blood pressure, long-term hypertension is often accompanied by target organ function or organic damage, which seriously affects people's health and quality of life. H$_2$S, on the other hand, relaxes myocardium and vascular smooth muscle in a variety of ways, thereby lowering blood pressure. First, H$_2$S induces phosphorylation of FOXO1 and FOXO3a by inhibiting endothelin-1 (ET-1), thereby promoting their nuclear translocation and binding to the target gene promoter. Furthermore, ATP sensitive potassium channel (KATP) was activated to significantly improve endothelium-dependent systolic function in hypertensive rats, promote vascular smooth muscle relaxation and relieve hypertension\textsuperscript{271}. Polhemus et al. found that some non-specific KATP blockers and mitochondrial MEMBRANE KATP channel blockers can reduce myocardial contractile force, this leads to increased cardiovascular load, which leads it is to increased blood pressure, while activation of the KATP channel reduces vascular load, which leads is in turn lowers blood pressure\textsuperscript{228}. In addition, Song Zhiqiang et al. stimulated Cl$^-$/ HCO$_3^-$ channel with NaHS to reduce intracellular pH value and increase H$^+$ concentration, thus activating
KATP channel, reducing vascular tension and alleviating hypertension\textsuperscript{[29]}. Third, regulate the balance of myocardial collagen fibers: Always there is a dynamic balance between the generation and degradation of myocardial collagen fibers to maintain the stability of collagen content. Once the collagen content in myocardium increases and the collagen configuration changes, myocardial fibrosis occurs. Homocysteine (Hcy) level is high in hypertensive patients, and high Hcy level can affect the balance of myocardial collagen regulation, leading to fibrosis of extracellular matrix of cardiomyocytes\textsuperscript{[30]}. Peng chao et al. pointed out that endogenous H$_2$S level can be used as a signal molecule of essential hypertension to reduce blood pressure and slow down heart rate\textsuperscript{[31]}.

3.4 H$_2$S and Heart Remodeling

Cardiac remodeling is characterized by ventricular dilatation, myocardial fibrosis, and heart failure. In recent years, there has been a significant increase in patients with heart failure in China. The myocardial protective effect of H$_2$S is a new research direction in the field of cardiovascular disease, providing a new idea for the treatment of heart failure. Liu et al.\textsuperscript{[32]} confirmed that H$_2$S can up-regulate endothelial NO level, thereby reducing stress load and preventing myocardial injury. Low levels of endogenous H$_2$S can lead to death in patients with heart failure\textsuperscript{[33]}. H$_2$S can inhibit myocardial hypertrophy and fibrosis by reducing the activity of angiotensin II and raised link 43 (Cx43) protein expression. Givvimani et al.\textsuperscript{[34]} found that H$_2$S can activate matrix metalloproteinases-2 (MMP-2) and inhibit matrix metalloproteinases-9 (MMP-9), thereby enhancing vascular endothelial growth factor (VEGF) synthesis and angiogenesis, reducing the level of anti-angiogenic factors, and reducing intracardiac fibrosis and heart remodeling in mice with pressure overload. In 2017, Wu et al.\textsuperscript{[35]} found that NaHS treatment could reduce myocardial cell apoptosis, interstitial fibrosis and cardiac hypertrophy in mice, and the overall survival rate of mice was relatively high, so it was speculated that exogenous H$_2$S had a good therapeutic effect on ischemic heart failure.

4. Summary and Prospect

A large number of studies have shown that H$_2$S, a gas signal molecule, has a myocardial protective effect on cardiovascular system diseases by inhibiting apoptosis, resisting Ca$^{2+}$ overload, anti-oxidative stress and so on. However, due to the narrow physiological range of H$_2$S and its extremely toxic effect, relevant research data are mainly from mouse and other animal model experiments, while human experiments are seldom carried out, so there is still a lack of strong clinical evidence. In addition, H$_2$S is also affected by statins, aspirin, metformin and other clinical drugs, making its clinical use more difficult\textsuperscript{[36]}. The mechanism of H$_2$S in protecting cardiomyocytes needs to be further explored, and how to regulate the concentration of exogenous H$_2$S for the treatment and prevention of cardiovascular diseases also needs to be further studied.

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