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ROLE OF HYDROGEN SULFIDE (H_2S) IN CELL SIGNALING AND ATHEROSCLEROSIS: A REVIEW

Mohd Izani Othman

Faculty of Pharmacy, Universiti Teknologi MARA Cawangan Pulau Pinang, Kampus Bertam, Persiaran Pendidikan Bertam Perdana, 13200 Kepala Batas, Pulau Pinang, MALAYSIA.
mohdizani.othman@ppinang.uitm.edu.my

ABSTRACT

Hydrogen sulfide (H_2S) has been known for decades as a toxic gas. However, this gas has been discovered to be synthesised enzymatically in human tissues and is regarded as a novel gasotransmitter. H_2S is a signaling molecule that involves and governs many biological functions of the body. It has been shown that H_2S is associated with various disease conditions such as acute pancreatitis, sepsis, inflammation and atherosclerosis development. Current therapeutic approach may not benefit all patients with atherosclerosis. Therefore, the role of H_2S as an anti-atherosclerotic agent has been the spotlight of cardiovascular medicine. Moreover, its implications in other diseases have also been studied extensively in order to develop new therapeutic approaches.

Keywords: hydrogen sulfide (H2S); atherosclerosis; reactive oxygen species (ROS); signaling molecule; oxidative stress; oxidised low density lipoprotein (oxLDL).

1. INTRODUCTION

Hydrogen sulfide (H_2S) is a colourless, flammable and poisonous gas with a characteristic rotten egg odour. This gas is present in the effluent of hydrothermal vents and sulphur springs and has long been known as a toxic pollutant (Mancardi et al., 2009). Interestingly, H_2S has been recognised as an important signalling molecule of the cardiovascular, inflammatory and immune systems (Wagner et al., 2009). It plays a vital role as a novel biologically active gas alongside with nitric oxide (NO) and carbon monoxide (CO) which involves in intracellular signalling processes (Song et al., 2014).

An increasing body of evidence has implicated the involvement of H_2S in biological systems through a variety of interrelated mechanisms (Szabo, 2007). In the past decade, H_2S has emerged as an important mediator in various physiological and pathophysiological processes (Whiteman et al., 2011). Studies have shown that H_2S can either protect or damage cells and this depends on its concentration, types of cell as well as experimental conditions (Wagner et al., 2009). High levels of H_2S are always accompanied by cytotoxic effects that could result from free radical generation and loss of glutathione (GSH). Low levels of H_2S have been shown to be either cytoprotective or proapoptotic (Adhikari & Bhatia, 2008).

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1.1 Biosynthesis and metabolism of H_2S

H_2S is enzymatically synthesised from amino acid cysteine, homocysteine and cystathionine by pyridoxal-5'-phosphate (PLP)-dependent enzymes such as cystathionine-β-synthase (CBS; E.C. 4.2.1.22) and cystathionine-γ-lyase (CSE; E.C. 4.4.1.1) (Whiteman et al., 2011). CBS and CSE are expressed in various locations including the brain, peripheral nervous system, liver, joint cells, intrauterine tissue, placenta and kidney (Whiteman et al., 2011). However, CBS is predominantly expressed in the brain and nervous system (Kimura, 2000) while CSE is mainly observed in vascular smooth muscle cells and in the heart (Zhao et al., 2001). It has also been proposed that 3-mercaptopyruvate sulfurtransferase (3-MST) which is an α-ketoglutarate and cysteine-dependent enzyme located in mitochondria (Shibuya et al., 2009) generates H_2S within the mitochondria (Modis et al., 2013a). 3-MST is also expressed in the brain and most of the H_2S produced by this enzyme is bound to the form of sulfane sulphur.

In vivo, H_2S is metabolised by oxidation in mitochondria or by methylation in cytosol and can be scavenged by methemoglobin or by metallo- or disulfide-containing molecules such as oxidised glutathione (Wang, 2003). H_2S is mainly excreted in the kidney as free or conjugated sulfate and as thiosulfate (Wang, 2003) and is also exhaled from the lungs.

1.2 Physiological and Pathophysiological Roles of H_2S

Various physiological effects of H_2S include as a major endothelium-derived hyperpolarising factor (EDHF) which causes hyperpolarisation and vasorelaxation of vascular endothelium and smooth muscle cells (Yang et al., 2008). As an antioxidant, H_2S can also prevent cytokine or oxidant-induced oxidative damage (Taniguchi *et al.*, 2011). Moreover, H_2S can also down-regulate NF-κB activation or up-regulate heme oxygenase 1 expression, thus inhibiting the expression of pro-inflammatory factors (Pan et al., 2011).

Pathophysiological role of H_2S has been implicated in many inflammatory and cardiovascular diseases (Bhatia, 2012). H_2S has been demonstrated to protect against oxidative injury in *in vivo* and *in vitro* models of myocardial ischemia-reperfusion models (Chen et al., 2007). Moreover, the inhibition of H_2S synthesis has been shown to accelerate the recovery of mean arterial pressure in a haemorrhagic shock model (Mok et al., 2004). Other beneficial effect of lowering H_2S levels was demonstrated in carrageenan-induced hindpaw edema (Bhatia et al., 2005b) and acute pancreatitis (Bhatia et al., 2005a).

1.3 H_2S as Reactive Oxygen Species (ROS) Scavenger and Inhibitor

H_2S is capable of scavenging free radicals by single electron or hydrogen atom transfer (Carballal et al., 2011). H_2S has been reported to scavenge reactive oxygen and nitrogen species such as superoxide (Yan et al., 2006), hydrogen peroxide (Lu et al., 2008), peroxynitrate (Whiteman et al., 2004), hypochlorous acid (Whiteman et al., 2005) and lipid hydroperoxides (Carballal et al., 2011).

In human endothelial cells (Muzaffar et al., 2008a) and vascular smooth muscle cells (Muzaffar et al., 2008b), H_2S has been demonstrated to inhibit superoxide production by reducing NADPH oxidase (NOX) expression and activity. Samhan-Arias et al. (2009) have also shown that H_2S protects synaptic plasma membranes from oxidative stress by the inhibition of ROS production via NOX.

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1.4 Roles of H_2S in the Mitochondria

Mitochondrion plays a vital role as the key source and target for detrimental intracellular oxidants generation (Murphy, 2009). Studies have implicated the importance of H_2S in regulating mitochondrial function (Modis et al., 2013a) as well as reducing mitochondrial ROS generation (Sun et al., 2012). Recent studies by Modis et al. (2013a) demonstrated that low levels of H_2S generated by mitochondrial enzyme, 3-MST, has donated electrons to the Krebs cycle, enhancing mitochondrial electron transport and bioenergetics. In hepatoma cells, this effect is suppressed during oxidative stress but reversed with administration of exogenous H_2S (Modis et al., 2013b).

In addition, translocation of CBS (Fu et al., 2012) and CSE (Modis et al., 2013b) from the cytosol to the mitochondrial matrix in response to hypoxic and calcium stress have also been observed. The resulting H_2S generation within the mitochondria might act as an electron acceptor in the mitochondrial respiratory chain which then increases cellular ATP production, thus preserving cell viability (Fu et al., 2012; Modis et al., 2013b).

1.5 H_2S Involvements in Intracellular Calcium Regulation

Calcium (Ca^{2+}) plays an important role as key signalling molecule in regulating various biological processes. Cytoplasmic concentration of Ca^{2+} is being tightly regulated within nanomolar range, which is approximately ten thousand fold difference across plasma membrane (1.5 mM at extracellular and 0.1 µM in cytosol) (Montell, 2005). Extracellular Ca^{2+} can cross plasma membrane via two major pathways i.e. voltage-operated Ca^{2+} channels (VOCCs) and receptor operated Ca^{2+} channels (ROCCs) (Pinilla *et al.*, 2005). Studies have demonstrated that H_2S has the capability of either inhibiting or activating Ca^{2+} entry and this depends on the molecular nature of the Ca^{2+} entry pathway [reviewed by Munaron et al. (2013)].

In exerting cardioprotective effect, it has been proposed that H_2S causes indirect inhibitory action on L-type calcium channels (VOCCs) besides directly inhibiting the β-adrenergic receptors (Mancardi et al., 2009). Thus, Sun et al. (2008) have shown the ability of H_2S to inhibit L-type calcium channels in NaHS treated rat cardiomyocytes whereas Maeda et al. (2009) have reported that H_2S may facilitate membrane currents through T-type calcium channels. In studies done on endothelial cells, Bauer et al. (2010) concluded that H_2S can directly regulate Ca^{2+} homeostasis and signalling via multiple mechanisms.

1.6 Roles of H_2S in Atherosclerosis

Atherosclerosis is characterised by multiple key events including endothelial dysfunction, infiltration of monocytes into the vascular wall and their differentiation into macrophages, uptake of oxidised low density lipoprotein (oxLDL) and conversion of lipid laden macrophages into foam cells and smooth muscle cell proliferation. Increasing evidence has implicated the significant involvement of H_2S in these biological processes and disruption of H_2S homeostasis may contribute to the pathogenesis of atherosclerosis (Lynn & Austin, 2011).

Recent studies have suggested that macrophages are able to produce H_2S endogenously (Zhu et al., 2010). Zhu et al. (2010) have reported the presence of CSE as well as endogenous H_2S

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production in peritoneal and RAW 264.7 macrophages treated with L-cysteine and PLP. They have also shown that lipopolysaccharide (LPS) stimulated CSE but not CBS expression and H_2S generation in macrophages.

Laggner et al. (2007) demonstrated that H_2S counteracts LDL oxidation by HOCl, whereby 50 µM HOCl was completely scavenged in the presence of equimolar concentrations of NaHS for 30 min at 37°C. In addition to its HOCl scavenging potential, the authors also found that H_2S inhibited myeloperoxidase (MPO) activity and scavenge H_2O_2. Studies done on HMDM cells by Zhao et al. (2011) revealed that NaHS treatment significantly suppressed macrophage derived foam cell formation by inhibiting oxLDL binding and uptake into macrophages. In addition, NaHS treatment significantly lowered the levels of CD36, scavenger receptor A and acetyl co-enzyme A acyltransferase-1 (ACAT1) expressions which were up-regulated by oxLDL in HMDM cells via KATP/ERK1/2 pathway.

1.7 H_2S Donors

Recently, several H_2S releasing molecules (termed as H_2S donors) have been developed to deliver a controlled and stable delivery of H_2S to cells and tissues. The development and characterisation of appropriate H_2S donors are vital for pharmacological use. H_2S donors should not be toxic, should be soluble in aqueous media, should not metabolise rapidly and should release H_2S *in vivo* slowly (Whiteman et al., 2011).

Although sulfide salts such as NaSH or Na_2S (Szabo, 2007) can be conveniently used to prepare standardised H_2S solution, they are not useful to be studied in H_2S physiology. This is because generation of both H_2S and Na^+ as an instantaneous release of bolus dissipates in a very short period of time (Li et al., 2008) rather than replicate the slow and sustained generation of H_2S from CSE, CBS or 3-MST enzymes in the tissues. Additionally, a huge and quick release of H_2S result in rapid fall of blood pressure which may have damaging effects in tissues or organs (Li et al., 2008).

Theferore, organic H_2S donors which generate H_2S in a physiologically-like manner were developed and synthesised (Whiteman et al., 2011) to avoid the use of sulfide salts. Existing non-steroidal anti-inflammatory drugs (NSAIDs) compounds such as indomethacin (ATB-343), diclofenac (ACS-15), naproxen (ATB-345) and mesalamine (ATB-429) (Whiteman & Winyard, 2011) have been modified by adding ADT-OH [5-(4-hydroxyphenyl-3H-1,2-dithiole-3-thione] group. Studies have shown that these organic H_2S donors actively alleviate and limit the adverse effects and toxicity of NSAIDs and demonstrate promising outcomes in treating inflammatory bowel disease, oedema, acute inflammation and endotoxic shock. Even though the precise mechanism of how ADT-OH releases H_2S is unknown (Whiteman et al., 2011), the potential therapeutic effects of ADT-OH derivatives in treating inflammatory and vascular disease as well as cancer is at least partly due to the release of H_2S (Whiteman et al., 2011).

The more recently synthesised and characterised H_2S donors do not consist of structurally modified established drug molecules such as GYY4137 (Whiteman et al., 2011). These water-soluble novel H_2S donors provide as pharmacological tools which generate H_2S at different rates. Recently, a novel dithiolethione derivative containing a triphenylphosphonium moiety (AP39) enabling specific delivery of sub-nanomolar concentrations of the compounds to mitochondria was also developed (Le Trionnaire et al., 2014).

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2. CONCLUSION

In recent years, there has been a significant development in the H_2S studies, particularly in health and disease. However, most of the studies on H_2S potentials have used sulfide salts. This might not be the best because of the rapid release of H_2S due to their high water solubility resulting in high local concentrations and lack of sustained effects. In contrast, slow releasing H_2S donors offer more reliable data regarding physiological effects of H_2S and provide potential opportunity for drug discovery including as possible candidates for treating atherosclerosis.

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