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Reprint of: Hydrogen sulfide in stroke: Protective or deleterious?☆,☆☆

Su Jing Chan [a, b, 1], Peter T.-H. Wong [c, *]

[a] Institute of Medical Biology, Agency for Science, Technology and Research (A*STAR), Singapore
[b] Departments of Radiology and Neurology, Massachusetts General Hospital, Harvard Medical School, USA
[c] Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

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ABSTRACT

Hydrogen sulfide is believed to be a signalling molecule in the central nervous system. It is known to increase rapidly following an ischemic insult in experimental stroke. Is it protective or deleterious? This review surveys the relevant information available in the literature. It appears that there is no definitive answer to this question at present. Current evidence seems to suggest that the presence of H_2S in the ischemic brain may either be deleterious or protective depending on its concentration, deleterious when high and protective when low. Therefore, it can be inferred that either an enhancement or a reduction of its concentration may be of potential use in future stroke therapy.

Contents

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Abbreviations: 3MST, 3-mercaptopyruvate sulfurtransferase; ADT, 5-(4-methoxyphenyl)-3H-1,2-dithiole-3-thione; AIF, apoptosis-inducing factor; Akt, protein kinase B; APAF-1, Apoptotic protease activating factor 1; Bax, Bcl-2-associated X protein; BBB, blood-brain-barrier; Bcl-2, B-cell lymphoma 2; BDNF, brain-derived neurotrophic factor; CBS, cystathionine β-synthase; CSE, cystathionine γ-lyase; Cys, cysteine; eIF2α, translational initiation factor 2α; ER, endoplasmic reticulum; grp78, 78 kDa glucose-regulated protein; γ-GCS, γ-glutamylcysteine synthetase; GSH, glutathione; Hcy, homocysteine; HIF-1α, hypoxia-inducible factor-1α; HSP70, heat shock protein 70; hyperHcy, hyperhomocysteinemia; IL, interleukin; iNOS, inducible nitric oxide synthase; MAPK, mitogen-activated protein kinase; MAT, Met S-adenosyltransferase; MDA, malon-dialdehyde; Met, methionine; MMP-9, matrix metallopeptidase; MTHFR, methylene-tetrahydrofolate reductase; mTOR, mechanistic target of rapamycin; Na_2S, sodium sulfide; NaHS, sodium hydrosulfide; NF-κB, nuclear factor-κB; NOX, nicotinamide adenine dinucleotide phosphate oxidase; Nrf2, nuclear factor-2; OGD, oxygen glucose deprivation; PARP-1, poly(ADP-ribose)polymerase-1; PERK, protein kinase-like endoplasmic reticulum kinase; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog; PTP, protein tyrosine phosphatase; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; SIRT-1, silent mating type information regulator 2 homolog 1; SOD, superoxide dismutase; SQR, sulfide-quinone oxidoreductase; pMCAO, permanent middle cerebral occlusion; tMCAO, transient middle cerebral occlusion; TNF-α, tumor necrotic factor α.

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* Corresponding author. Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, 16, Medical Drive, #04-01, 117600 Singapore.
E-mail address: peter_wong@nuhs.edu.sg (P.T.-H. Wong).
[1] Present address: Departments of Radiology and Neurology, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129, USA.

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1. Introduction

In the past 2 decades or so, hydrogen sulfide (H_2S) has been transformed from a toxic gas with an offensive odour to a gasotransmitter (Wang, 2002) with important functional roles in major organ systems such as the cardiovascular (Geng et al., 2004; Bian et al., 2006; Liu et al., 2012) and central nervous systems (CNS) (Abe and Kimura, 1996; Abe and Kimura, 1996; Liu et al., 2012; Tan et al., 2010). While there seems to be a general consensus that H_2S plays a protective role in the cardiovascular system (CVS) (Lavu et al., 2011; Dongo et al., 2011; Ji et al., 2008; Lavu et al., 2011; Lefer, 2007; Sodha et al., 2009; Szabó et al., 2011), there is controversy in the ischemic brain. Is it protective or deleterious in stroke? This short review attempts to decipher the information available in the current literature.

2. H_2S is an endogenous molecule with physiological functions

H_2S, a colourless toxic gas well known for its rotten egg smell, was described way back in the early eighteenth century (Ramazzini, 1713). H_2S has emerged as an endogenous signalling molecule produced in many tissues in mammalian species (Hosoki et al., 1997; Linden et al., 2008; Doeller et al., 2005; Kamoun, 2004; Renga, 2011; Shibuya et al., 2013). It is water soluble and, at physiological pH, approximately 70% are ionized to hydrosulfide anion (HS^-) with an insignificant amount of sulfur anion (S^{2-}) (Reiffenstein et al., 1992; Cuevasanta et al., 2016). H_2S is slightly hydrophobic and twice as soluble in lipid membranes as in water, thus it can rapidly traverse plasma membranes and diffuse between compartments, such as from cytoplasm to mitochondria where it can be oxidized (Cuevasanta et al., 2016).

H_2S can be found in many tissues, including heart, liver, blood and brain. H_2S levels measured in biological tissues had been decreasing with improved measuring techniques and advancement in technology. It was previously reported that the H_2S concentration in the brain was as high as 50–160 μM (Goodwin et al., 1989; Warenycia et al., 1989; Mitchell et al., 1993; Yu et al., 2015). Ishigami et al. (2009) reported 9 μM, using a method that is likely to be superior to the traditional methylene blue assay by avoiding the possibility of measuring acid labile sulfur. However low H_2S levels of about 14 nM has also been measured in the mouse brain using gas chromatography (Furne et al., 2008). More recently, the endogenous level of free H_2S in the brain has been measured at 0.12 nmol/g protein which is thousands of folds lower than the levels of acid-labile H_2S at about 900 nmol/g protein (Levitt et al., 2011). However, as H_2S will be released from its acid-labile sulfur pool only when mitochondrial pH falls below 5.4, the acid-labile sulfur pool is not likely to be a main source of H_2S release at physiological pH (Kimura, 2015). On the other hand, H_2S can be released from bound sulfane sulfur localized in cytoplasm under both reducing and acidic conditions. It is widely believed that H_2S release from the bound sulfane sulfur is regulated by the redox status in the cytoplasm (Kimura, 2015). In view of the low free H_2S levels measured, Levitt et al. (2011) suggested that it may not directly influence tissue metabolism in the brain. However, as H_2S is known to have a high turnover rate with an estimated half-life of 10 min in brain homogenate (Vitvitsky et al., 2012), the possibility of H_2S involving in normal brain physiology cannot be ruled out. The physiological roles of H_2S in the CNS have been described (Abe and Kimura, 1996; Bos et al., 2015). It may function as a neuromodulator regulating ion channels and tyrosine kinase activities (Abe and Kimura, 1996; Liu et al., 2012). Furthermore, several pathophysiological roles of H_2S has been widely studied in CNS diseases, for example Parkinson disease (Hu et al., 2010; Kida et al., 2011; Tang et al., 2011), Alzheimer's disease (Barbaux et al., 2000; Fan et al., 2013; Giuliani et al., 2013; Morrison et al., 1996), Huntington's disease (Paul et al., 2014) and ischemic stroke (Qu et al., 2006; Wong et al., 2006).

3. H_2S biosynthesis in the brain

H_2S biosynthesis is closely linked to the transulfuration pathway through which, homocysteine (Hcy) is converted by cystathionine β-synthase (CBS, EC. 4.2.1.22) to cystathionine, which is then converted to cysteine (Cys) by cystathionine γ-lyase (CSE, EC. 4.4.1.1) (Qu et al., 2008). H_2S is known to be synthesized endogenously by three enzymes, namely CBS, CSE and 3-mercaptopyruvate sulfurtransferase (3MST, EC. 3.4.1.2) in conjunction with cysteine aminotransferase (EC 2.6.1.3) (Kabil and Banerjee, 2014). CBS and CSE have drawn much interest and are better understood. CSE, which produces H_2S from Cys, can be found in abundance in the cardiovascular system (Bian et al., 2006) and its mRNA levels were previously reported in the myocardium (Geng et al., 2004), endothelial cells (ECs) (Yang et al., 2008) and smooth muscle cells (SMCs) (Zhao et al., 2001). The expression of CSE was confirmed to be minor in the brain and in support, CSE inhibitor was shown not to suppress the production of H_2S in the rat brain (Abe and Kimura, 1996; Bian et al., 2006). $CSE^{-/-}$ mice developed symptoms like spontaneous hypotension (Geng et al., 2004), lethal myopathy and were more susceptible to oxidative stress with Cys deficient diet (Ishii et al., 2010). Recently, Jiang et al. (2015) reported that CBS is upregulated in the cerebral cortex of $CSE^{-/-}$ mice following MCA ligation. Moreover, they also reported that L-cysteine-induced H_2S production was increased in the ischemic cortex, when compared to the contralateral control, to the same extent in both control and $CSE^{-/-}$ mice.

While CBS is strongly expressed in the brain, there are some conflicting observations with respect to the cellular localization of this enzyme. Using in situ hybridization and Northern blot, Robert et al. (2003) found that the expression of CBS was strongest in the Purkinje cell layer and hippocampus. Immunohistochemical staining indicated that CBS localization in most parts of the mouse brain and predominantly in the cell bodies and neuronal process of Purkinje cells and Ammon's horn neurons. Enokido et al. (2005) confirmed the ubiquitous presence of CBS but reported intense expression of CBS in the cerebellar molecular layer and hippocampal dentate gyrus. They further reported that CBS is also preferentially expressed in cerebellar Bergmann glia and in astrocytes throughout the brain. This was supported by the presence of a