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Hydrogen sulphide in cardiovascular system: A cascade from interaction between sulphur atoms and signalling molecules

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ABSTRACT

As a gasotransmitter, hydrogen sulphide exerts its extensive physiological and pathophysiological effects in mammals. The interaction between sulphur atoms and signalling molecules forms a cascade that modulates cellular functions and homeostasis. In this review, we focus on the signalling mechanism underlying the effect of hydrogen sulphide in the cardiovascular system and metabolism as well as the biological relevance to human diseases.

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1. Introduction

The complicated human body is built from basic elements, including carbon, hydrogen, nitrogen, oxygen, phosphorus and sulphur. To date, little is known about the role of the element sulphur in physiology and diseases. It is established that sulphur is essential in sulphur-containing amino acids, which are one of the elemental components of cells. Some of the sulphur molecules form hydrogen sulphide (H_2S) *in vivo*, which plays essential roles in signal transduction as a gasotransmitter [1–3].

In mammalian tissues, H_2S is synthesised mainly by endogenous enzymes, namely cystathionine beta-synthase (CBS) and cystathionine gamma-lyase (CSE) in cytoplasm, and 3-mercaptopyruvate sulphurtransferase primarily in mitochondria. Newly synthesised H_2S is removed quickly by degradation for adequate signalling.

The permeability of a given molecule through a cell membrane lipid bilayer determines its target specificity and mechanism of action. H_2S transports across cell membranes by simple diffusion; no intramembrane channels (e.g. aquaporins) are needed [4]. A mathematical model raised by Cuevasanta suggests that H_2S produced by a single cell expands to involve more than 200 neighbouring cells, whereas lipid membranes add some resistance to the diffusion at physiological pH, thus supporting the paracrine role of H_2S [5].

The targets of H_2S are quite diverse. H_2S interacts with reactive oxygen and nitrogen species and alters their generation or competes at downstream signalling [6,7]; it influences gene expression by regulating transcription factors [8–10]; it alters the function of intracellular and membrane proteins, including ion channels, kinases and receptors [11–16]; it binds to metal centres or electron transfer with metal centres of enzymes and thus change their activity [17–19].

Underlying the majority of the above functions are the atomic biology, the interaction between sulphur atoms and signalling molecules. Different models have been proposed [16,20], and both involve the attack of sulphur atoms in H_2S to sulphur atoms in cysteine residues of target molecules.

Firstly, in the present review, we discuss in detail fundamental H_2S atomic biology-how small molecules regulate the big ones. Secondly, we move to the molecular level and summarise the genes and proteins that participate in H_2S-regulated cardiovascular function. Thirdly, we summarise the influence of H_2S to major cell types in the cardiovascular system. Lastly, several physiological processes, including angiogenesis, cardioprotection, metabolism and vascular ageing, are examined from an integrated point of view.

2. H_2S atomic biology: interactions between sulphur atoms and signalling molecules

2.1. The functional form of H_2S and signalling molecules derived from H_2S

H_2S has high water solubility. It dissolves and dissociates into H^+, HS^- and S^{2-}. However, the functional form with physiological relevance is not well understood yet. In a normal internal environment (pH 7.4), approximately 20% of the total H_2S is H_2S gas; the remaining 80% exists in the HS^- form with trace amount of S^{2-} [21].

Other forms of sulphur (e.g. sulphane sulphur) derived from H_2S are more stable and may be responsible for some H_2S functions [21,22]. At a physiological pH, HS^- autoxidises to sulphane sulphur, and the conversion is favoured in an alkaline or oxidative condition [22,23]. Formed sulphane sulphur can be reduced to H_2S by glutathione and other thiols [24]. By this means, some protective effect of garlic [25] may be mediated by H_2S.

2.2. How H_2S interacts with other signalling molecules

Although H_2S penetrates cell membranes by simple diffusion, its precise influence towards numerous important biological processes requires functional specificity. This apparent discrepancy gives rise to a fundamental question in H_2S biology: How does H_2S interact with other signalling molecules? What are the direct target molecules for H_2S?

(1) Disulphide bond opening

H_2S is a reducing agent; it may reduce the cysteine disulphide bond and lead to conformational changes in proteins. Tao first identified vascular endothelial growth factor receptor 2 (VEGFR2) as a direct target molecule mediating the proangiogenic effect of H_2S [16]. She found a molecular switch, the Cys1024-S-S-Cys1045 disulphide bond, located in the intracellular kinase domain of VEGFR2, which serves as a targeting motif labile to H_2S regulation. H_2S specifically breaks this inhibitory disulphide bond in the VEGFR2 intracellular kinase core and causes subsequent conformational and functional change of VEGFR2. A VEGFR2 mutant, C1045A, prevents the formation of disulphide bonds and significantly increases the kinase activity. Molecular dynamic simulations reveal that the Cys1024-S-S-Cys1045 disulphide bond interferes with adenosine triphosphate (ATP) binding to the intracellular kinase core and turns it into its inactive conformation. By breaking this disulphide bond, H_2S shifts the intracellular kinase core into its active conformation [16].

Quantum chemical calculations point to a two-step reaction that requires two H_2S molecules to break one disulphide bond. Electrospray ionisation mass spectrometry experiments support this two-step theory by identifying an intermediate S-sulfhydrated cysteine (Cys-S-SH) that transiently formed and disappeared before the end of the reaction. This intermediate was formed by attacking of the first H_2S molecule to a cysteine residue composing a functional disulphide bond then disappeared due to the attack of a second H_2S molecule. No S-sulfhydration in the kinase domain of VEGFR2 was found, and none of the tested 20 free amino acids undergoes chemical modification by overdose sodium hydrosulphide (NaHS) treatment in a cell-free system [16].

Regulation via molecular switches by H_2S is distinguished from that of the typical mechanisms of ligand-receptor docking. The latter one is based on conformational matching between a ligand and its receptor; however, H_2S is too small to have a conformation for docking. Regulation via molecular switches is actually an interaction between two sulfur atoms (i.e. the sulphur atom in an H_2S molecule attacks the sulphur atom molecular switch inside a target, via nucleophilic attack).

Despite the difference in extracellular ligand binding domains among members of the receptor tyrosine kinase family, the structures of intracellular kinase domains are similar. This prompted the authors to examine the role of H_2S in other members of the receptor tyrosine kinase family and led to the finding about the role of H_2S in regulating the insulin receptor (IR). H_2S increases the phosphorylation of IR and glucose uptake, ameliorates glucose metabolism in a type 2 diabetic animal model and protects kidney function. Moreover, H_2S directly activates IR in a cell-free system [15].

Recently, Ge confirmed the direct interaction between H_2S and epidermal growth factor receptor (EGFR). H_2S induces cleavage of some disulphide bonds in the EGFR intracellular kinase domain, and activates the EGFR/gab1/PI3K/Akt pathway. Cys798 in the intracellular kinase domain of EGFR is required for H_2S regulation [14].

The readers need to be aware that not all the functional disulphide bonds are sensitive to H_2S. For example, the increased activity of γ-glutamylcysteine synthetase upon H_2S treatment is probably mediated by other intracellular signalling molecules, but not the functional disulphide bond [26] in the enzyme, because a direct effect of H_2S is absent [27].

(2) Cysteine residue modification

In addition to the disulphide bond-breaking theory, another widely accepted mechanism of H_2S signalling is protein sulfhydration, the