Pharmacological Reports 67 (2015) 647–658

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Review article

Hydrogen sulfide in pharmacology and medicine – An update

Jerzy Bełtowski

Department of Pathophysiology, Medical University, Lublin, Poland

ARTICLE INFO

Article history:
Received 3 December 2014
Accepted 5 January 2015
Available online 22 January 2015

Keywords:
Hydrogen sulfide
Gasotransmitters
Non-steroidal anti-inflammatory drugs
Cardiovascular diseases
Inflammation

ABSTRACT

Hydrogen sulfide (H_2S) is the endogenously produced gasotransmitter involved in the regulation of nervous system, cardiovascular functions, inflammatory response, gastrointestinal system and renal function. Together with nitric oxide and carbon monoxide, H_2S belongs to a family of gasotransmitters. H_2S is synthesized from L-cysteine and/or L-homocysteine by cystathionine β-synthase, cystathionine γ-lyase and cysteine aminotransferase together with 3-mercaptopyruvate sulfurtransferase. Significant progress has been made in recent years in our understanding of H_2S biochemistry, signaling mechanisms and physiological role. H_2S-mediated signaling may be accounted for not only by the intact compound but also by its oxidized form, polysulfides. The most important signaling mechanisms include reaction with protein thiol groups to form persulfides (protein S-sulfhydration), reaction with nitric oxide and related species such as nitrosothiols to form thionitrous acid (HSNO), nitrosopersulfide ($SSNO^-$) and nitroxyl (HNO), as well as reaction with hemoproteins. H_2S is enzymatically oxidized in mitochondria to thiosulfate and sulfate by specific enzymes, sulfide:quinone oxidoreductase, persulfide dioxygenase, rhodanese and sulfite oxidase. H_2S donors have therapeutic potential for diseases such as arterial and pulmonary hypertension, atherosclerosis, ischemia–reperfusion injury, heart failure, peptic ulcer disease, acute and chronic inflammatory diseases, Parkinson's and Alzheimer's disease and erectile dysfunction. The group of currently available H_2S donors includes inorganic sulfide salts, synthetic organic slow-releasing H_2S donors, H_2S-releasing non-steroidal antiinflammatory drugs, cysteine analogs, nucleoside phosphorothioates and plant-derived polysulfides contained in garlic. H_2S is also regulated by many currently used drugs but the mechanism of these effects and their clinical implications are only started to be understood.

Contents

E-mail addresses: jerzy.beltowski@umlub.pl, jerzybel@hotmail.com.

http://dx.doi.org/10.1016/j.pharep.2015.01.005
1734-1140/

Introduction

It was first proposed by Abe and Kimura in 1996 that hydrogen sulfide (H_2S) is the endogenously generated neuromodulator [1]. During almost two decades since their seminal paper was published, a large body of data about H_2S in biological systems has been accumulated. Currently, there is little doubt that hydrogen sulfide is the third "gasotransmitter" in addition to nitric oxide (NO) and carbon monoxide (CO) [2–4]. In 2007 we published a review article about H_2S in pharmacology in this journal [5]. Herein, I briefly review the progress made in the field since that time. Because H_2S literature is now very huge, I will not comprehensively cover its effects in all experimental systems but will focus on general aspects of H_2S biochemistry and molecular signaling mechanisms as well as its potential application in pharmacotherapy.

General properties of H_2S

H_2S is a colorless flammable gas with a strong odor of rotten eggs. It is easily soluble in both water and lipids. At physiological pH (7.4) less than 20% of H_2S exists in the solution as the undissociated compound and the rest is dissociated to HS^- (hydrosulfide anion) and H^+. Further dissociation of HS^- to sulfide anion (S^{2-}) occurs only at high pH and is insignificant at physiological conditions. Since both H_2S and HS^- always coexist in aqueous solution, it is not possible to separate their effects and to conclude which of them is involved in signaling processes [6]. From the chemical point of view, H_2S is the simplest thiol and as such is a reductant. It should be noted that pK_a of H_2S (6.8) is by 1–2 units lower than of most allylthiol species (R–SH) present *in vivo* such as glutathione (GSH) or protein cysteine thiols (CysSH); consequently, a greater portion of H_2S exists in the dissociated form than of other thiols. Hydrosulfide anion (HS^-) is easily oxidized to hydrosulfide radical ($HS^\bullet$) which is the oxidizing species [6].

It has been known for a long time that so called sulfane sulfur, that is sulfur atoms at zero oxidation step usually bound only to other sulfur atoms, exists in tissues [7,8]. One of the forms of sulfane sulfur are protein persulfide (perthiol, hydrodisulfide, Cys–SSH) and hydropolysulfide ($CysS_nH$, $n > 2$) groups, glutathione persulfide (GSSH) or polysulfide (GS_nH) as well as inorganic polysulfides (HS_nH). Some recent studies suggest that these forms of sulfane sulfur may contribute to H_2S signaling (see below) [9].

Endogenous H_2S synthesis

Four enzymatic pathways of H_2S production have been described so far. Two of them are catalyzed by cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) which are pyridoxal 5′-phosphate (vitamin B_6)-dependent cytosolic enzymes of the transsulfuration pathway in which homocysteine is metabolized to cysteine. In the transsulfuration pathway L-homocysteine is condensed by CBS with L-serine to produce L-cystathionine and H_2O. However, L-serine may be replaced in this reaction by L-cysteine with L-cystathionine and H_2S being the products (Table 1). Nevertheless, because L-cysteine is less abundant in the intracellular compartment than L-serine and K_m of CBS for L-serine is lower than for L-cysteine, H_2S production is less efficient than canonical transsulfuration reaction catalyzed by this enzyme [10]. CBS may also catalyze the alternative reactions between two cysteine or two homocysteine residues to form H_2S and lanthionine (two cysteine molecules connected by thioether –S– bond) or homolanthionine (two homocysteine molecules connected by the –S– bond), respectively [11]. CBS is a tetrameric protein; each subunit consist of N-terminal catalytic domain containing heme, substrate-, and PLP-binding sites, whereas C-terminal regulatory domain binds the positive allosteric regulator, S-adenosylmethionine. NO and CO reduce CBS activity by binding to its heme group which is the important mechanism of interplay between these gasotransmitters. In particular, CO binds to the CBS heme moiety with high affinity [12–14].

In the transsulfuration pathway, CSE breaks down L-cystathionine to L-cysteine, α-ketobutyrate and ammonia. Some of the reactions catalyzed by CBS in which H_2S is produced are also shared by CSE, but the main mechanisms of H_2S production by this enzyme seems to be β-elimination of L-cysteine or γ-elimination of L-homocysteine to ammonia, H_2S and pyruvate or α-ketobutyrate, respectively (Table 1) [15]. Because L-cysteine concentration exceeds that of L-homocysteine, cysteine desulfhydration is the main mechanism of H_2S production by CSE under physiological conditions [16]. Importantly, increase in homocysteine concentration increases total H_2S production by CSE and the contribution of homocysteine-involving reactions [15]. In contrast, CBS-catalyzed H_2S production is not affected by homocysteine concentration. However, these relationships were mainly examined in the *in vitro* models. Although H_2S has been demonstrated to ameliorate some of the negative effects of homocysteine, the impact of hyperhomocysteinemia on H_2S production *in vivo* has not been studied so far.

In general it is suggested that CBS is the main H_2S synthase in the nervous system whereas CSE plays this role in most peripheral tissues except the liver and kidney which contain both enzymes in substantial amounts. The role of CBS may be underestimated in experiments in which only L-cysteine is used as the substrate because, to produce H_2S, CBS requires both L-cysteine and L-homocysteine to be present simultaneously [11].

Recently, it has been demonstrated that both CBS and CSE can break down L-cystine (cysteine disulfide) to thiocysteine (CysSSH, cysteine persulfide), pyruvate and ammonia [17]. Through further exchange reactions between CysSSH and glutathione or protein cysteine thiols, the respective persulfide species (GSSH and protein-CysSSH) may be formed. It is suggested that this kind of sulfane sulfur may operate as the signaling species instead of H_2S itself and that H_2S may just be the marker of persulfide compounds released through their reaction with reductants [17]. However, because cytosolic L-cystine/L-cysteine ratio is normally very low, the contribution of this reaction to overall H_2S/sulfane pool is unclear. Nevertheless, as L-cystine may be transported to the cell through cystine-glutamate antiporter, it can achieve significant concentrations at the vicinity of plasma membranes. In addition, L-cystine/L-cysteine ratio increases in oxidative stress-related