UDC 612.17 https://doi.org/10.15407/biotech13.06.024

GASOMEDIATOR H_2S IN THROMBOSIS AND HEMOSTASIS

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Received 24.10.2020
Revised 13.12.2020
Accepted 30.12.2020

This review was aimed to briefly summarize current knowledge of the biological roles of gasomediator H_2S in hemostasis and cardiovascular diseases. Since the discovery that mammalian cells are enzymatically producing H_2S, this molecule underwent a dramatic metamorphosis from dangerous pollutant to a biologically relevant mediator. As a gasomediator, hydrogen sulfide plays a role of signaling molecule, which is involved in a number of processes in health and disease, including pathogenesis of cardiovascular abnormalities, mainly through modulating different patterns of vasculature functions and thrombotic events. Recently, several studies have provided unequivocal evidence that H_2S reduces blood platelet reactivity by inhibiting different stages of platelet activation (platelet adhesion, secretion and aggregation) and thrombus formation. Moreover, H_2S changes the structure and function of fibrinogen and proteins associated with fibrinolysis. Hydrogen sulfide regulates proliferation and apoptosis of vascular smooth muscle cells, thus modulating angiogenesis and vessel function. Undoubtedly, H_2S is also involved in a multitude of other physiological functions. For example, it exhibits anti-inflammatory effects by inhibiting ROS production and increasing expression of antioxidant enzymes. Some studies have demonstrated the role of hydrogen sulfide as therapeutic agent in various diseases, including cardiovascular pathologies. Further studies are required to evaluate its importance as a regulator of cell physiology and associated cardiovascular pathological conditions such as myocardial infarction and stroke.

Key words: hydrogen sulfide, gasomediator, hemostasis, thrombosis, fibrinolysis, platelets, cardiovascular diseases.

H_2S: from toxin to biological mediator

For many decades, hydrogen sulfide (H_2S), a simple gaseous molecule with the smell of rotten eggs, was considered to be a toxic gas that penetrates cells by simple diffusion [1]. Generations of researchers have investigated the toxicological effects of H_2S in various species, including human. Among the more recent studies: Attene-Ramos demonstrated the genotoxic effect of high doses of H_2S [2], Nicholson [3], Khan [4] and later Dorman [5] have directly showed the inhibition of cytochrome c oxidase activity *ex vivo* in tissues after H_2S exposure of experimental animals, and implicating these effect s in the disruption of respiratory and mitochondrial functions in the mammalian brain (and other tissue). It is currently accepted that H_2S exerts its toxicological actions on the molecular level primary through the inhibition of mitochondrial Complex IV. Via this action, the consumption of O_2 is limited and mitochondrial electron transport and ATP generation is blocked. However, the toxicological mode of H_2S action is more complex, as it is capable of interacting with multiple intra- and extracellular proteins (for instance, sulfhydration etc.).

Following the discovery that mammalian cells are capable of producing H_2S, this molecule underwent a dramatic metamorphosis of recognition from dangerous pollutant to a biologically relevant molecule (as NO). Three enzymes have been shown to enzymatically

generate H_2S, cystathionine β-synthase (CBS), cystathionine γ-lyase (CTH or CSE) and 3-mercaptopyruvate sulfurtransferase (3MST) [6–8]. CBS and CSE participate in the interconversion of homocysteine to cysteine, known as the transsulfuration pathway; both enzymes are pyridoxal-5 phosphate dependent [9, 10]. It should, however, be kept in mind that CBS and CSE catalyze number of additional reactions that do not yield H_2S [9]. The gene expression of CBS and CSE has been detected in various tissues, including the liver, kidney, lymphatic system, vascular wall, cardiomyocytes and fibroblasts. While these enzymes contribute equally to the local production of H_2S in liver and kidney [11], one of the enzymes could be dominant in other contexts. There is prevalence of CSE in cardiovascular system [12]. Relatively high concentration of CSE is observed in arteries, and H_2S is produced by both endothelial cells [13] and smooth muscle cells of the vessel wall [14]. The key enzyme for H_2S synthesis in the central and peripheral nervous system is CBS [15].

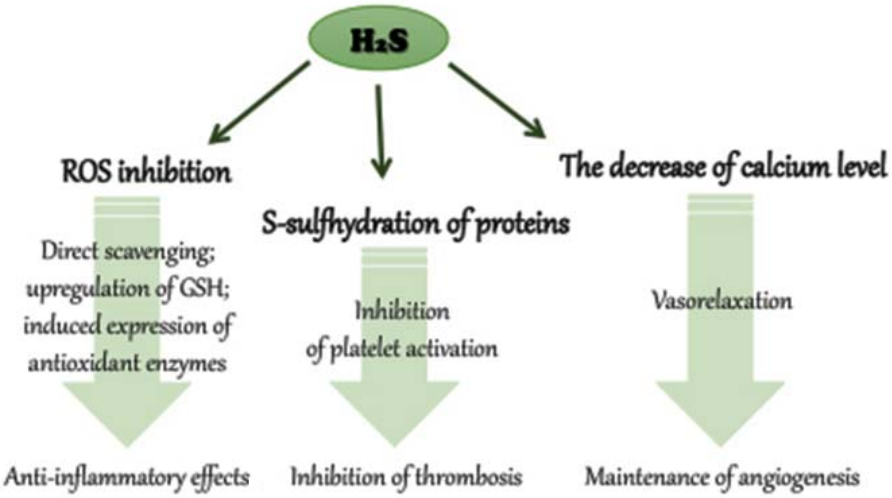
H_2S dissolved in water is a weak acid and dissociates into H^+, HS^-, and S_2^-. At physiological pH (7.4), such as in blood and other physiological solutions, approximately 14% of the free sulfides are present as gaseous H_2S, more than 80% is present as HS^-, and the rest is S_2^-. It is still undetermined, which form is biologically active. H_2S itself, HS^-, polysulfides, as well as S/N hybrid species have been shown to affect a variety of signaling pathways leading to biological responses [16, 6, 17]. Hydrogen sulfide is also soluble in lipid membranes so that it has access to both intracellular and extracellular sites of target proteins [18]. A primary mechanism through which H_2S affects the activity of signaling proteins is a modification of reactive cysteine SH groups to persulfide groups (-SSH) [19]. This posttranslational modification is similar to S-nitrosylation, which is induced by NO, and could be an important signaling mechanism. Depending on the nature of the targeted protein, the effect of H_2S might take from seconds to days to manifest.

The field of H_2S biology has dramatically expanded over the last decade. Now endogenous hydrogen sulfide is recognized as a gasomediator of various physiological and pathological processes [1]. H_2S has been proven to be involved in vascular relaxation, hypertension, cellular proliferation, gene expression, cardioprotection, neuroprotection, intestinal secretion, diabetes, apoptosis, atherosclerosis and inflammation.

H_2S in vascular biology and thrombosis

Endogenous concentrations of hydrogen sulfide in human plasma are ranged from 30 μM to 65 μM [20]. Its physiological level in brain is threefold higher than in serum [21]. However, H_2S concentration in human tissues depends on the method used for measurement and the donor's age [20]. The primary action of H_2S in the vasculature is vasodilatory [6, 10, 1]. Although, biphasic responses to H_2S have been reported [22]. The first reports on vasoactive responses to endogenous H_2S were from Kimura's group, where they demonstrated the presence of H_2S-producing enzymes in vascular tissue, and showed the smooth muscle relaxant effect of H_2S, alone and in synergy with nitric oxide [23]. Latter studies, from Wang's laboratory demonstrated the importance of KATP for H_2S-triggered vasorelaxation [14]. Based on its ability to hyperpolarize endothelial and smooth cell membrane, its biological activity on small and/or intermediate conductance KCa channels, and its greater potency as a vasodilator in resistance versus conduit arteries, H_2S has been proposed as a candidate for endothelium-derived hyperpolarizing factor [24, 25]. Various groups have shown the protective effect of H_2S in organ injury and postischemic reperfusion disorders [26]. H_2S contributes to the maintenance of mean arterial blood pressure at physiological levels; pharmacological inhibition of H_2S production was shown to increase blood pressure [27]. Several laboratories have confirmed that H_2S drives angiogenesis by stimulating EC growth, motility, and organization into vessel-like structures [28–30]. Enhanced oxidative stress is a key event for diseases affecting the vessel wall including hypertension, atherosclerosis, and vascular diabetic complications. Hydrogen sulfide exhibits anti-inflammatory effects by inhibiting ROS production, but also eliminates ROS by direct scavenging, upregulation of GSH, and increased expression of antioxidant enzymes [31–33]. It was observed that H_2S causes apoptosis of human aortic smooth muscle cells and reduces the growth of atherosclerotic lesions [34].

Recent studies showed that H_2S exerts antithrombotic properties by inhibiting different steps of platelet activation (platelet adhesion, secretion and aggregation) and thrombus formation [35–39]. First it was demonstrated that NaHS (H_2S donor) prevented in a concentration-dependent manner human platelet aggregation induced



Gasomediator H_2S in vascular biology and thrombosis

by different agonists: ADP, U46619, collagen, epinephrine, thrombin and arachidonic acid [36]. Results of Nishikawa et al. showed that H_2S suppresses rabbit platelet aggregation (induced by collagen and ADP) by interfering with both upstream and downstream signals of cytosolic Ca^{2+} mobilization in cAMP-dependent manner [37]. Experiments of Grambow et. al. suggested that the anti-aggregatory effect of hydrogen sulfide might be due to S-sulfhydration of blood platelet proteins [39]. Next study demonstrated the inhibitory action of H_2S on blood platelet adhesion [38]. Moreover, hydrogen sulfide modifies the adhesive properties of collagen and fibrinogen [39]. The authors assume that the interaction of modified adhesive proteins may cause impaired adhesion [39]. Other research group observed that H_2S-releasing aspirin derivative ACS14 exerts strong antiaggregatory effects *in vitro* and *in vivo* via impairing the activation of fibrinogen receptor by mechanism involving increased intracellular cyclic nucleotides [40]. The study of Kram et al. has shown that H_2S has antithrombotic action, i.e. prolonging the time until both initial occlusion of blood flow. It was concluded that the anti-thrombotic efficacy of H_2S involves the NOS pathway [41].

The effects of hydrogen sulfide on the complex coagulation system and fibrinolysis are manifold due to its pleiotropic character. Olas and Kontek reported that activated partial thromboplastin time (APTT), prothrombin time (PT) and thrombin time (TT) of plasma treated with NaHS (H_2S donor) are prolonged *in vitro* [42]. The reduced fibrin polymerization of plasma in the presence of NaHS was also observed [42]. These results indicate the anticoagulant activities of H_2S. Modifications of various proteins of hemostatic system (including fibrinogen, plasminogen, and thrombin) induced by H_2S may be associated with changes of coagulation process and fibrinolysis. Other researchers demonstrated that compound with thiol group(s) enhances plasma factor XIII-mediated fibrinogen cross linking [43, 44]. It is possible that H_2S is involved in this process.

Some studies have demonstrated the role of hydrogen sulfide as therapeutic agent in various diseases, including cardiovascular diseases. An injectable Na_2S (IK-1001), which is H_2S donor, has been developed for clinical use [45]. S-allylcystein, which may be derived from garlic, reduced blood platelet aggregation, and this action may be mediated through H_2S [46]. Some proposal mechanisms of H_2S actions in vascular biology and thrombosis are summarized in Figure.

Hydrogen sulfide is a ubiquitous signaling molecule with important functions in many mammalian organs and systems. Although some beneficial properties of H_2S in hemostasis and thrombosis are well established, mechanistic insights into the molecular pathways implicated in disease prevention and treatment remain largely unexplored. In addition, acute regulation of H_2S production is still poorly understood and new researches delineating the pathways regulating the enzymes that produce H_2S will allow pharmacological manipulation of these pathways.

Funding: University of Texas Medical Branch (UTMB), Galveston, TX, USA.

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ГАЗОМЕДІАТОР H_2S У ТРОМБОЗІ ТА ГЕМОСТАЗІ

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Метою огляду було стисло підсумувати наявні дані стосовно біологічної ролі газомедіатору сульфіду гідрогену в гемостазі та за розвитку серцево-судинних захворювань. Після відкриття здатності клітин ссавців ензиматично продукувати H_2S погляди на значення цієї молекули кардинально змінювалися: від віднесення його до небезпечних токсинів до визнання біологічно важливим регулятором. Як газомедіатор сульфід гідрогену відіграє роль сигнальної молекули, що залучається до низки процесів за норми та патології, включно з патогенезом серцево-судинних порушень, головним чином, модулюючи переважно різні аспекти функціонування судин та тромботичні явища. Нещодавно було отримано беззаперечні докази пригнічення сульфідом гідрогену активності тромбоцитів, що спостерігається на різних стадіях їх активації (тромбоцитарна адгезія, секреція та агрегація), а також власно формування тромбу. Більш того, H_2S модифікує структуру і функцію фібриногену та протеїнів системи фібринолізу. Сульфід гідрогену регулює проліферацію та апоптоз клітин гладеньких м'язів, модулюючи у такий спосіб ангіогенез і функціонування судин. Не викликає сумнівів, що H_2S також залучається до реалізації низки інших фізіологічних функцій. Наприклад, він виявляє протизапальні ефекти через інгібування утворення активних форм оксигену та підсилення експресії антиоксидантних ензимів. У деяких дослідженнях висвітлено роль сульфіду гідрогену як терапевтичного агента за різних захворювань, зокрема патологій серцево-судинної системи. Подальшого з'ясування потребує значення цього газомедіатору як регулятора клітинної фізіології за розвитку серцево-судинних хвороб, зокрема, інфаркту міокарда та інсульту.

Ключові слова: сульфід гідрогену, газомедіатор, гемостаз, тромбоз, фібриноліз, тромбоцити, серцево-судинні хвороби.

ГАЗОМЕДИАТОР H_2S В ТРОМБОЗЕ И ГЕМОСТАЗЕ

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Целью обзора было вкратце подытожить существующие сведения о биологической роли газомедиатора сульфида водорода в гемостазе и при развитии сердечно-сосудистых заболеваний. После открытия способности клеток млекопитающих энзиматически производить H_2S взгляды на значение этой молекулы кардинально изменялись: от отнесения его к опасным токсинам до признания биологически важным регулятором. Как газомедиатор сульфид водорода играет роль сигнальной молекулы, вовлекаемой в ряд процессов при норме и патологии, включая патогенез сердечно-сосудистых нарушений, модулируя главным образом различные аспекты функционирования сосудов и тромботические явления. Недавно были получены неопровержимые доказательства подавления сульфидом водорода активности тромбоцитов, наблюдаемые на разных стадиях их активации (тромбоцитарная адгезия, секреция и агрегация), а также собственно формирование тромба. Более того, H_2S модифицирует структуру и функцию фибриногена и протеинов системы фибринолиза. Сульфид водорода регулирует пролиферацию и апоптоз клеток гладких мышц, модулируя таким образом ангиогенез и функционирование сосудов. Не вызывает сомнений, что H_2S также участвует в реализации ряда других физиологических функций. Например, он проявляет противовоспалительные эффекты, ингибируя образование активных форм кислорода и усиливая экспрессию антиоксидантных энзимов. В некоторых исследованиях освещены роль сульфида водорода в качестве терапевтического агента при различных заболеваниях, в частности патологий сердечно-сосудистой системы. Дальнейшего выяснения требует значение этого газомедиатора как регулятора клеточной физиологии при развитии сердечно-сосудистых заболеваний, в частности инфаркта миокарда и инсульта.

Ключевые слова: сульфид водорода, газомедиатор, гемостаз, тромбоз, фибринолиз, тромбоциты, сердечно-сосудистые заболевания.