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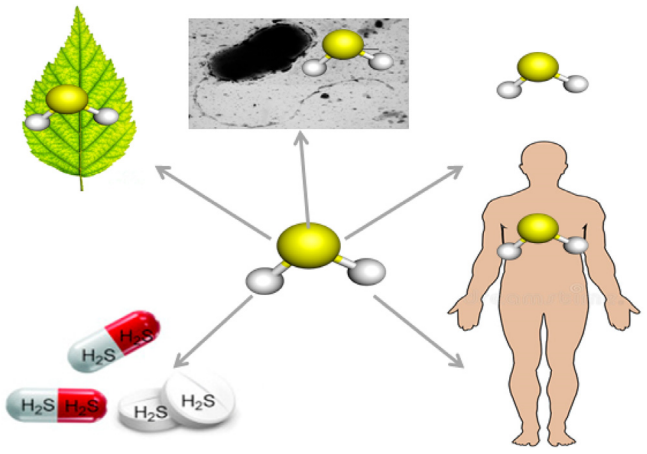
Editorial Note on the Special Issue: Chemistry, biology and clinical applications of the third gasotransmitter, hydrogen sulfide (H_2S)



Hydrogen sulfide (H_2S) is currently considered among the endogenously produced gaseous molecules that exert various signaling effects in mammalian species. It is the third physiological gasotransmitters discovered so far after NO and CO. H_2S was originally ranked among the toxic gases at elevated levels to humans. Currently, it is well-known that, in the cardiovascular system, H_2S exerts several cardioprotective effects including vasodilation, antioxidant regulation, inhibition of inflammation, and activation of anti-apoptosis. There is growing number of studies that make use of the stable donors of H_2S for the development of pharmacologically active cardiovascular agents. New roles of H_2S in the pathophysiology of cancer have also emerged. The field of H_2S is now booming in different directions. In this awakening move, JAR is delighted to contribute in highlighting the importance of this molecule in chemistry, biology and medicine and to shed more lights on the mechanisms of its action and potential roles in drug development and therapeutics.

The focus of this special issue is to highlight the most updates on the role of hydrogen sulfide in various biological systems and its novel detection methods. We would like to thank all authors who submitted their work in this Special Issue. After the reviewing phases by top researchers in the field, 18 papers were accepted. These papers are performed through the academic collaboration of researchers from different countries represented by leading researchers in the field of H_2S. A brief synopsis of these papers is provided below.

In the research paper "***Point-of-care testing and optimization of sample treatment for fluorometric determination of hydrogen sulphide in plasma of cardiovascular patients***", a new biological sample treatment study is detailed for optimum selective determination of the unionized form of H_2S in blood of CVD patients using a new in-house POCT portable spectrofluorometer together with a reagent-analyser system. The study is novel in being a POCT approach for selective determination of H_2S molecular form in plasma after simple optimized sample treatment. The study confirms that MI is associated with elevated H_2S levels up to 10 h from emergence of symptoms.

In the review paper "***Hydrogen sulfide: Recent progress and perspectives for the treatment of dermatological diseases***" recent progress and novel perspectives are outlined to the reader on the role of H_2S in the treatment of dermatological diseases. Three H_2S production enzymes, cystathionine-c-lyase (CSE), cystathionine-b-synthase (CBS) and 3-mercaptopyruvate sulfur transferase (3-MST), are expressed differentially in the skin according to the type of skin cell. Previous discussed studies have demonstrated that H_2S protects against several dermatological diseases, such as burns, diabetic skin wounds, psoriasis, skin flap transplantation, systemic sclerosis, melanoma, and pruritus. Potential H_2S novel targets for therapeutic intervention and drug design for skin disorders are presented, which may lead to the development and application of H_2S -related drugs for dermatological diseases.

The aim of the review paper "***Hydrogen sulfide regulates insulin secretion and insulin resistance in diabetes mellitus, a new promising target for diabetes mellitus treatment? A review***", is to summarize and discuss current data about the function of H_2S in insulin secretion and insulin resistance regulation as well as the underlying mechanisms. H_2S is endogenously produced in pancreatic islet β cells, liver, adipose, skeletal muscles, and the hypothalamus, and to regulate local and systemic glucose metabolism. It is reported that H_2S suppresses insulin secretion, promotes or reduces the apoptosis of islet β cells. It also plays important roles in the regulation of insulin sensitivity in insulin responsive tissues. The review highlights H_2S potential as a new promising target for diabetes mellitus treatment.

The protective role of H_2S in cognitive impairment in diabetic rats is presented in the research entitled ***"Hippocampal ornithine decarboxylase/spermidine pathway mediates H2S-alleviated cognitive impairment in diabetic rats: Involving enhancment of hippocampal autophagic flux***" This paper assessed the roles of hippocampal ODC/Spd pathway and autophagic flux in H2S-attenuated cognitive impairment in STZ-induced diabetic rats. Sodium hydrosulfide (NaHS, a donor of H_2S) markedly improved the autop-

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hagic flux in the hippocampus of STZ-exposed rats, as evidenced by a decrease in the number of autophagosomes as wells as downregulations in the expressions of LC3-II, Beclin-1, and P62 in the hippocampus of cotreatment with NaHS and STZ rats. NaHS also upregulated the expression of ODC and the level of Spd in the hippocampus of STZ-induced diabetic rats. Furthermore, inhibited hippocampal ODC/Spd pathway by difluoromethylornithine (DFMO) markedly reversed the protections of NaHS against the hippocampal autophagic flux impairment as well as the cognitive dysfunction in STZ-exposed rats.

In the research paper "***Structure-activity relationships study of isothiocyanates for H2S releasing properties: 3-Pyridyl-isothiocyanate as a new promising cardioprotective agent***", a library of forty-five isothiocyanates, selected for their different chemical properties, has been evaluated for its H_2S releasing capacity. The obtained results allowed to correlate several factors such as steric hindrance, electronic effects and position of the substituents to the observed H_2S production. Moreover, the chemical-physical profiles of the selected compounds have been studied by an *in silico* approach and from a combination of the obtained results. 3-pyridyl-isothiocyanate has been selected as the most promising one. A detailed pharmacological characterization of its cardioprotective action has been performed. The results strongly support 3-pyridyl-isothiocyanate as a suitable pharmacological option in anti-ischemic therapy.

The meta-analysis paper "***Hydrogen sulfide toxicity in the gut environment: Meta-analysis of sulfate-reducing and lactic acid bacteria in inflammatory processes***", presents a systematic review that provides important information about the development of gut inflammation, with emphasis on sulfate-reducing and lactic acid bacteria. Oppositely from sulfate-reducing bacteria, probiotic properties of lactic acid bacteria are effective inhibitors against inflammatory bowel disease development, including ulcerative colitis. This fact was confirmed by the conducted meta-analysis. The results and observations gained from the systematic review emphasize the importance of gut microbiota for protection from bowel inflammation.

In the research paper "***Possible synergy effect of hydrogen sulfide and acetate produced by sulfate-reducing bacteria SRB on inflammatory bowel disease development***", processes concerning sulfate reduction microbial metabolisms were investigated, including main microbial genera monitoring and their hydrogen sulfide production in the intestines of healthy and ill individuals, phylogenetic analysis of SRB isolates, cluster analysis of SRB physiological and biochemical parameters, SRB growth kinetic parameters calculation, same as the application of the two-factor dispersion analysis for finding relationship between SRB biomass accumulation, temperature and pH. Feces samples from healthy people and patients with colitis were used for isolation of sulfate-reducing microbial communities. Microbiological, biochemical, biophysical, molecular biology methods, and statistical processing of the results have been used for making an evaluation of gained results and proof of hypothesis. The study results provide novel insights concerning colony environments with developed colitis and these findings can lead to the development of possible risk indicators of ulcerative colitis prevalence.

In the review paper "***Abnormalities of hydrogen sulfide and glutathione pathways in mitochondrial dysfunction***" the current knowledge regarding the possible connections between mitochondrial disorders and alteration of hydrogen sulfide metabolism is presented. Mitochondrial disorders are genetic diseases for which therapy remains woefully inadequate. Therapy of these disorders is particularly challenging partially due to the heterogeneity and tissue-specificity of pathomechanisms involved in these disorders. Abnormalities in hydrogen sulfide (H_2S) metabolism are emerging as novel mechanism in mitochondrial dysfunction. Future studies are highlighted to better understand the effects, protective or detrimental, of these abnormalities, and their relevance, in mitochondrial diseases.

The review paper "***Hydrogen sulfide and vascular regulation – An update***", summarizes and discusses current data about the function of H_2S in vascular physiology and pathophysiology as well as the underlying mechanisms. The mechanisms underlying H_2S-induced vasodilation included H_2S induced vasorelaxation predominantly by activating iron channels, interacting with NO-cGMP signaling, inhibiting mitochondrial complex I and III, and acting as an adipocyte-derived relaxing factor (ADRF). In addition, H2S inhibits the proliferation of VSMCs in association with MAPK/ TXNIP, Brg1, ERK1/2, IGF-1R and CaSR signals The review highlights the need for further studies to investigate the interaction amongst H2S and other gaseous signaling molecules including NO and sulfur dioxide (SO2). The study suggests that drugs targeting H2S producing enzymes (CBS, CSE and 3-MST) merits further clinical research.

A complementary review on H_2S role in endothelial dysfunction and therapeutic applications is presented in a review entitled "***Role of hydrogen sulfide in endothelial dysfunction: Pathophysiology and therapeutic approaches***". The role of hydrogen sulfide in endothelial dysfunction-related cardiovascular diseases is discussed in this review. Possible therapeutic approaches using molecules able to release H2S are presented to the reader to represent a useful tool in the protection of endothelial cells in different pathological conditions. Further clinical studies are suggested to involve receiving H_2S-donors patients affected by those pathologies that lead to ensothelial dysfunction.

Likewise, a research paper on the role of H_2S in endothelial function is presented entitled "***Endogenous hydrogen sulfide improves vascular remodeling through PPARd/SOCS3 signaling***" This study aimed to investigate the beneficial role of H_2S on vascular remodeling using CSE inhibitor, DL-propargylglycine (PPG), treated mice and vascular smooth muscle cells (VSMCs). The deficiency of endogenous H_2S generated vascular remodeling with aggravated active and passive contraction, thicken aortic walls, collagen deposition, increased phosphorylation of STAT3, decreased production of PPARd and SOCS3 in aortas, which were reversed by sodium hydrosulfide (NaHS) chronic treatment. PPG inhibited expression of PPARd and SOCS3, stimulated the phosphorylation of STAT3, increased inflammatory molecules production and proliferation rate of VSMCs which could all be corrected by NaHS supply. PPARδ agonist GW501516 offered protections similar to NaHS in PPG treated VSMCs. Aggravated active and passive contraction in PPG mice aortas, upregulated p-STAT3 and inflammatory molecules, downregulated SOCS3 and phenotype transformation in PPG treated VSMCs could be corrected by PPARd agonist GW501516 treatment.

The review paper "***Implications of hydrogen sulfide in liver pathophysiology: Mechanistic insights and therapeutic potential***", summarizes on the recent advances in the cellular events triggered by H2S under liver diseases. The therapeutic effects of H_2S donors on hepatic diseases will also be discussed. Key scientific concepts of review include a critical regulator of liver functions, H_2S is critically involved in the etiology of various liver disorders, such as nonalcoholic steatohepatitis (NASH), hepatic fibrosis, hepatic ischemia/reperfusion (IR) injury, and liver cancer. Targeting H_2S -producing enzymes is presented to researchers as a promising strategy for managing hepatic disorders.

With regards to H_2S detection and quantification methods, a review article is presented entitled "***Emerging analytical tools for the detection of the third gasotransmitter H_2S, a comprehensive review***" discusses the several analytical technologies used for H2S determination including spectroscopic, chromatographic, and electrochemical methods. Advantages and limitations with regard to the application of each technique are highlighted with special

emphasis on its employment for H_2S *in vivo* measurement in biofluids and tissues. Despite a myriad of developed analytical procedures used for H_2S determination, the need for highly selective, highly sensitive, biocompatible, reproducible, and accurate H_2S measurement methods seems imperative to untangle the non-resolved pitfalls of the current methods.

The research paper "***Persulfidation of transcription factor FOXO1 at cysteine 457: A novel mechanism by which H2S inhibits vascular smooth muscle cell proliferation***", assesses whether H_2S persulfidates the transcription factor FOXO1 to inhibit vascular smooth muscle cells (VSMCs) proliferation. The proliferation of VSMCs is an important physiological and pathological basis for many cardiovascular diseases. Endogenous H2S is found to preserve vascular structure by inhibiting VSMC proliferation. However, the mechanism by which H_2S suppresses VSMC proliferation has not been fully clear. The results showed that endothelin-1 (ET-1) stimulation increased cell proliferation, FOXO1 phosphorylation and FOXO1 nuclear exclusion to the cytoplasm in the cells. However, pretreatment with NaHS, an H_2S donor, successfully abolished the ET-1-induced increases in the VSMC proliferation, FOXO1 phosphorylation, and FOXO1 nuclear exclusion to the cytoplasm. Mechanistically, H_2S persulfidated the FOXO1 protein in A7r5 and 293 T cells, and the thiol reductant DTT reversed this effect. This research demonstrated that H_2S might inhibit VSMC proliferation by persulfidating FOXO1 at Cys457 and subsequently preventing FOXO1 phosphorylation at Ser256.

The research paper "***Hydrogen sulfide inhibits aortic valve calcification in heart via regulating RUNX2 by NF-jB, a link between inflammation and mineralization***" investigated whether H_2S inhibits mineralization via abolishing inflammation. Expression of pro-inflammatory cytokines, interleukin-1 (IL-1) and tumor necrosis factor (TNF-) were increased in patients with calcific aortic valve disease (CAVD) and in calcified aortic valve of ApoE-/- mice. Administration of H_2S releasing donor (4-methoxyphenyl piperidinylphosphinodithioc acid (AP72)) inhibited both calcification and inflammation in aortic valve of apolipoprotein E knockout mice (ApoE-/-) mice as reflected by lowering IL-1 and TNF- levels. Accordingly, AP72 prevented the accumulation of extracellular calcium deposition and decreased nuclear translocation of nuclear factor-B (NF-B) in human valvular interstitial cells (VIC). Double-silencing of endogenous H_2S producing enzymes, cystathionine gamma-lyase (CSE) and cystathionine beta-synthase (CBS) in VIC exerted enhanced mineralization and higher levels of IL1 and TNF-. Employing Stimulated Emission Depletion (STED) nanoscopy, a strong colocalization of NF-B and Runx2 was detected during the progression of valvular calcification. This paper presents that H_2S inhibits inflammation and calcification of aortic valve. The study suggests that the regulation of Runx2 by hydrogen sulfide (CSE/CBS) occurs *via* NF-B establishing a link between inflammation and mineralization in vascular calcification.

With regards to H_2S oncogenic properties, a research paper entitled "***Targeting hydrogen sulphide signaling in breast cancer***" investigated the role of H_2S in breast cancer (BC) pathogenesis, on BC immune recognition capacity and the consequence of targeting H_2S using non-coding RNAs. Eighty BC patients have been recruited for the study. BC cell lines were cultured and transfected using validated oligonucleotide delivery system. Gene and protein expression analysis was performed using qRT-PCR, western blot and flow-cytometry. In-vitro analysis for BC hallmarks was performed using MTT, BrdU, Modified Boyden chamber, migration and colony forming assays. H_2S and nitric oxide (NO) levels were measured spectrophotometrically. Primary natural killer cells (NK cells) and T cell isolation and chimeric antigen receptor transduction (CAR T cells) were performed using appropriate kits. NK and T cells cytotoxicity was measured. Finally, computational target prediction analysis and binding confirmation analyses were performed using different software and dual luciferase assay kit, respectively. This study demonstrates the potential role of H_2S signaling in BC pathogenesis and the potential of its targeting for disease mitigation.

A research article discussed the role of H_2S *in plants* entitled "***The coordination of guard-cell autonomous ABA synthesis and DES1 function in situ regulates plant water deficit responses***". It demonstrated the potential crosstalk between L-cysteine desulfhydrase 1 (DES1)-dependent H2S and phytohormone abscisic acid (ABA) signaling in response to dehydration and its regulation mechanism. By introducing guard cell-specific MYB60 promoter, to produce complementary lines of DES1 or ABA3 into guard cell of des1 or aba3 mutant. The related genes expression and water loss under ABA, NaHS, or dehydration treatment in these mutant or transgenics lines were determined. dehydration-induced expression of DES1 was abolished in the abscisic acid deficient 3 (aba3) mutants that were deficient in ABA synthesis. Both the complementation of ABA3 expression in guard cells of the aba3 mutants and ABA treatment rescued the dehydration-induced expression of DES1, as well as the wilting phenotype observed in these mutants. These results demonstrate that the coordinated synthesis of ABA and DES1 expression is required for drought-induced stomatal closure in Arabidopsis.

A second article that link H_2S to plants is presented in the review article entitled "***Something smells bad to plant pathogens: production of hydrogen sulfide in plants and its role in plant defence responses***" that focuses on the biosynthesis of H_2S in plant cells, with special attention to L-cysteine desulfhydrase (DES) as the key enzyme controlling H_2S levels biosynthesis in the cytosol of plant cells during plant growth, development and diverse abiotic and biotic stress conditions. Recent advances revealed molecular mechanisms of DES properties, functions and regulation involved in modulations of H_2S production during plant responses to abiotic and biotic stress stimuli. Studies on des mutants of the model plant Arabidopsis thaliana uncovered molecular mechanisms of H_2S action as a signalling and defense molecule in plant-pathogen interactions. Signalling pathways of H_2S include S-persulfidation of protein cysteines, a redox-based post-translational modification leading to activation of downstream components of H_2S signalling. Presented knowledge on the molecular mechanisms of H_2S action in plant defense responses opens new prospects in the search for crop varieties with increased resistance to bacterial and fungal pathogens.

The guest editors would like to express their thanks and appreciation to all the submitting authors for considering this special issue as a forum for publishing their research work. The assistance of the reviewers, through their high-quality reports, was very helpful for choosing the papers which are suitable for this Special Issue. Our expectation is that the content of this special issue will attract the interest of the researchers which are involved in H_2S emerging role in biology and therapeutics, and to help them for advancing that field steps forward. We do sincerely hope our readers find it of value and interest.

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