

BIO-MEDICAL IMPORTANCE OF HYDROGEN SULFIDE FOR BALNEOLOGY: MECHANISMS AND CLINICAL SIGNIFICANCE

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Relevant Financial Disclosure(s)

Funding: "This work was supported by a grant of the Ministry of Research, Innovation and Digitization, CCCDI - UEFISCDI, project number PN-III-P2-2.1-PED-2021-2146, within PNCDI III"



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No. Inregistrare UEFISCDI 11/01/2022

CONTRACT DE FINANTARE
PENTRU EXECUTIE PROIECTE

NR. 649PED / 2022

Finantare: Institut de stat
Denumirea Programului din PN III: Programul 2 - Creșterea competitivității economiei românești prin cercetare, dezvoltare și inovare
Denumirea Subprogramului: Subprogramul 2.1 - Competitivitate prin cercetare, dezvoltare și inovare
Tip proiect: Proiect experimental - demonstrativ
Titlul proiectului: Metoda combinată bazată pe imagistică hiperspectrală și investigații biologice de evaluare a efectelor unor factori naturali terapeuți în afecțiuni din sfera patologiei Neuro-Mio-Arto-Kinetice

Valoarea totală a Contractului: 508.795,00 lei
Din care, pe surse:
Sursa 1 - de la bugetul de stat: 508.795,00 lei
Sursa 2 - din alte surse atrase (cofinanțare): 0,00 lei
Durata contractului: 24 luni
Nr. de pagini ale contractului: 24 pagini
Autoritatea Contractantă: Unitatea Executivă pentru Finanțarea Investițiilor Smerșor, a Cercetării, Dezvoltării și Inovării UNIVERSITATEA DE MEDICINA SI FARMACIE "GRIGORE T. POPA" DIN IASI

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Data: 24.05.2022
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Raport științific și tehnic

Etapă de execuție nr. 1 / 2022

Contract nr.: 649PED/2022

Etapă nr. 1/2022: Dezvoltarea metodei BIOHIS

Cod proiect: PN-III-P2-2.1-PED-2021-2146

Titlul proiectului: Metoda combinată bazată pe imagistică hiperspectrală și investigații biologice de evaluare a efectelor unor factori naturali terapeuți în afecțiuni din sfera patologiei Neuro-Mio-Arto-Kinetice (BIOHIS)

- Descrierea științifică cu punerea în evidență a rezultatelor etapelor anuale și graful de realizare a obiectivelor;

Etapă 1 din cadrul proiectului BIOHIS are ca obiectiv principal dezvoltarea unei noi metode de biogenerare - metoda BIOHIS - dedicată evaluării eficienței terapiei a factorilor terapiei naturali cum sunt nămolul sau apele minerale sulfuroase naturale asupra diferitelor patologii Neuro-Mio-Arto-Kinetice (NMAK). Metoda BIOHIS se bazează pe combinarea informațiilor furnizate de tehnica de imagistică hiperspectrală (HSI) cu date obținute din investigații biologice care se concentrează la evidențierea cantitativă a efectelor factorilor terapiei naturali și utilizarea lor ca remedii naturale pentru patologia NMAK. Imagistica hiperspectrală (HSI) este o tehnica emergentă în domeniul medical care integrează facilitățile oferite de imagistica digitală și spectroscopia pentru a colecta simultan atât informații spațiale cât și spectrale despre un țesut/organ care permit o descriere fină a structurii/compoziției chimice a țesuturilor investigate ce poate fi utilă medicilor în procesul de diagnosticare sau monitorizare a tratamentelor medicale. Posibilitatea utilizării combinate a unor astfel de informații spectrale-spațiale furnizate de tehnica HSI cu date obținute din investigații biologice este explorată în cadrul dezvoltării metodei BIOHIS propuse în acest proiect. Factorii terapiei naturali, precum nămolul și apele terapeuți minerale sulfuroase, sunt utilizați în scopuri și clinici de recuperare prin băi sau aplicații topice pe corp pentru multe afecțiuni din sfera patologiei Neuro-Mio-Arto-Kinetice.



Combined method based on hyperspectral imaging and biological investigations to evaluate the effects of natural therapeutic factors in diseases in the field of Neuro-Mio-Arto-Kinetic pathology

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649PED din 24/06/2022
(PN-III-P2-2.1-PED-2021-2146)

CONSTANTIN MUNTEANU

METODA COMBINATĂ BAZATĂ PE IMAGISTICĂ HIPERSPECTRALĂ ȘI INVESTIGAȚII BIOLOGICE DE EVALUARE A EFECTELOR UNOR FACTORI NATURALI TERAPEUTICI ÎN AFECȚIUNI DIN SFERA PATOLOGIEI NEURO-MIO-ARTRO-KINETICE [BIOHIS]

1. UNIVERSITATEA DE MEDICINA SI FARMACIE "GRIGORE T. POPA" DIN IASI
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- The medical relevance of **therapeutic gases** can range from use in burns and stroke victims to hypoxia therapy.
- **Medical gases** such as **oxygen, hydrogen, helium and xenon** have recently come under increased exploration for their potential therapeutic use in various brain disease states, including traumatic brain injuries, hypoxia-ischemia, and cerebral hemorrhages.
- This **synthetic review** aims to rigorously select related articles and identify within their content the main possible uses of therapeutic gases and physiological mechanisms.
- Therapeutic gases are not fully understood and used adequately for sanogenic or medical purposes. More research is needed to fully understand the mechanisms and importance of therapeutic gases. The link between balneotherapy and medical rehabilitation regarding the usage of therapeutic gases emphasises the unity for this medical speciality.








Therapeutic gases used in balneotherapy and rehabilitation medicine - scientific relevance in the last ten years (2011 – 2020) - Synthetic literature review

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Balneo and PRM Research Journal DOI: <http://dx.doi.org/10.12680/balneo.2021.430> Vol.12, No.2, June 2021 p. 111-122

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Abstract

Background. The medical relevance of therapeutic gases can range from use in burns and stroke victims to hypoxia therapy in children. However, medical gases such as oxygen, hydrogen, helium and xenon have recently come under increased exploration for their potential therapeutic use on various brain disease states, including traumatic brain injuries, hypoxia-ischemia and, cerebral hemorrhages.

Objective. This synthetic review aims to rigorously select related articles and identify within their content the main possible uses of therapeutic gases and physiological mechanisms. The objective of this article is to present the various therapeutic mechanisms that have been proposed in the current literature and the medical relevance of various therapeutic gases used in balneotherapy or medical rehabilitation.

Methods. To elaborate our synthesis review, we have searched for relevant open access articles in 6 international databases: Cochrane¹, Elsevier¹, NCBI/PubMed¹, NCBI/PMC¹, PEDro¹, and ISI Web of Knowledge/Science¹, published from January 2011 until December 2020. The contextually queried keywords combinations/ syntaxes used specified on this page. The eligible articles were analyzed in detail regarding pathologies addressed by therapeutic gases. All articles with any design (reviews, randomized controlled trials, non-randomized controlled trials, case-control studies, cross-sectional studies), if eligible according to the above-mentioned selection methodology, containing in the title or abstract the above-mentioned combinations, were included in the analysis. Articles were excluded in the second phase if they did not reach the relevance criterion.

Results. Our search identified, first, **225** articles. After eliminating the duplicates, remained **180** articles. In the second phase, we applied a relevance criterion. Although our team - including the authors of this paper - have quite long and consistent expertise in achieving systematic literature reviews, the marked heterogeneity of both the item composing the subject we have approached and inherently the wase of presentations in the respective quite vast and diverse domain of medical gases, prevented us to fulfil, at least regarding this initial work, a systematic literature review. Instead, we succeeded to make a hopefully interesting and valuable narrative synthetic-related literature review. At the end of the second phase, **63** articles passed the relevance criterion and were included in this synthetic review.

Conclusions. Therapeutic gases are not fully understood and used adequately for sanogenic or medical purposes. More research is needed to fully understand the mechanisms and importance of therapeutic gases. The link between balneotherapy and medical rehabilitation regarding the usage of therapeutic gases emphasises the unity for this medical speciality.

Keywords: "Therapeutic gas"/ "Oxygen therapy"/ "Carbon dioxide"/ "CO2 therapy"/ "Carbon monoxide"/ "Mofette"/ "Hydrogen Sulfide"/ "H2S"/ "Helium"/ "Xenon"/ "Ozone therapy"/ "Radon"/ "Hydrogen therapy"/ "Nitric oxide"/ "Heliox" AND "Rehabilitation".

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Assist. prof. dr. Gabriela Dogaru, Ph.D. Priority research areas: balneoclimatology, including the study of carbonated mineral waters and mofettes, molecular and cellular medicine, e-health systems, neurological and cardiovascular rehabilitation, development of spa, and rehabilitation tourism

Assoc. prof. dr. Mariana Rotariu, Ph.D. - Kinesiology, Psychomotricity, psychomotor education and reeducation, Kinesiotherapy, Kinesiotherapy, Massage, Complementary techniques, Occupational therapy, Rehabilitation, and techniques of functional reeducation

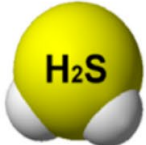
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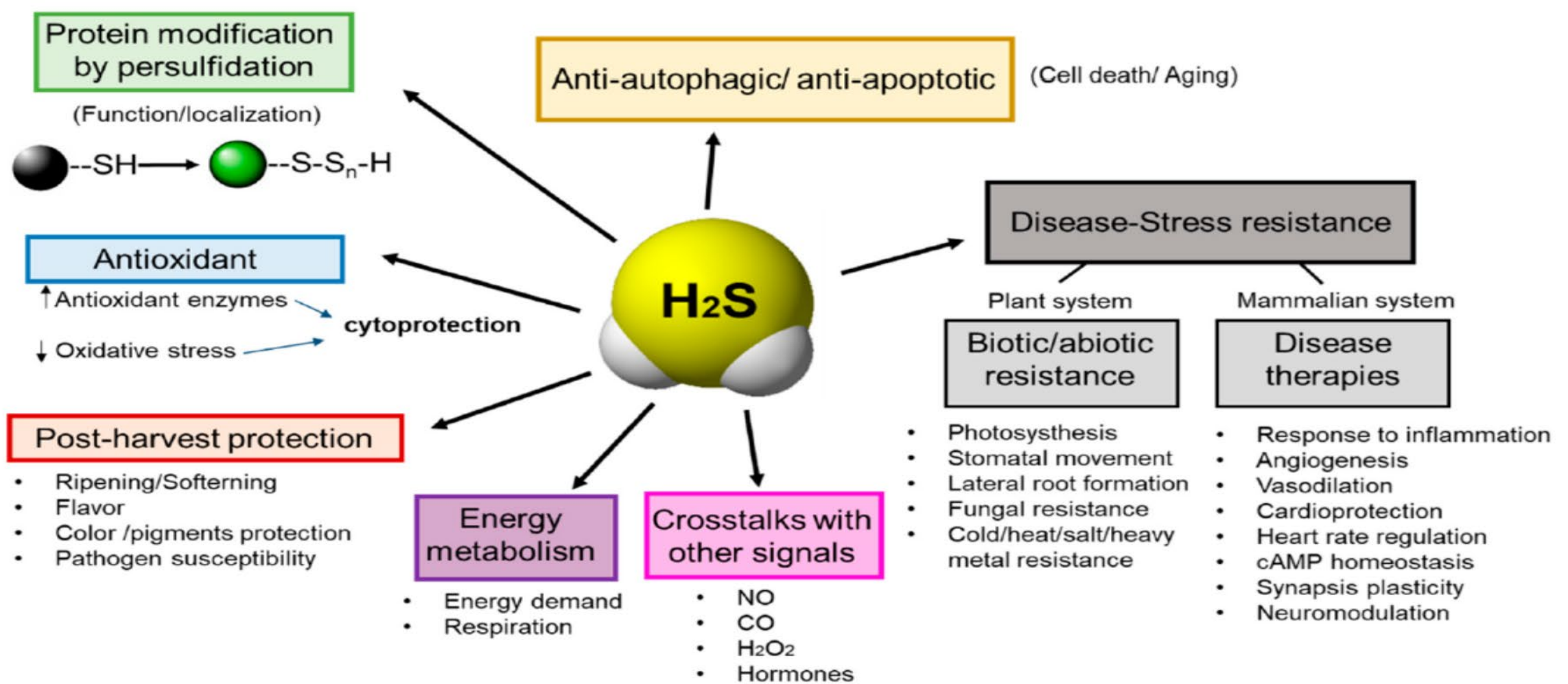



Hydrogen sulfide, or H₂S, has a very particular scientific history. For a long time, it was regarded almost exclusively as a toxic gas, associated with the characteristic smell of rotten eggs, industrial exposure, and environmental hazard. Today, however, this molecule has acquired a completely different meaning in biology and medicine. Together with nitric oxide and carbon monoxide, H₂S is now recognized as an endogenous gasotransmitter, a small gaseous signaling molecule involved in vascular regulation, redox balance, inflammation, mitochondrial function, cellular protection, neuromodulation, and tissue adaptation. At the same time, H₂S is also an exogenous therapeutic factor encountered in sulfurous mineral waters and therapeutic muds, which are central elements of traditional and contemporary balneology. This dual nature is precisely why H₂S is so relevant for our field: it connects molecular biology with natural therapeutic resources.

Nitric oxide, carbon monoxide, and hydrogen sulfide are all small molecules with high membrane permeability, short biological half-lives, and broad signaling effects. However, they differ in enzymatic production, molecular targets, concentration ranges, and clinical translation. Nitric oxide is already used therapeutically in several contexts and is indirectly targeted by drugs such as phosphodiesterase inhibitors. Carbon monoxide has cytoprotective effects but remains clinically difficult because of toxicity. Hydrogen sulfide is in a similar translational phase: mechanistically promising, clinically intriguing, but still requiring careful dosing, safety, and evidence-based validation.

								
Name	Hydrogen sulfide		Nitric oxide		Hydrogen peroxide		Carbon monoxide	
Chemical formula	H-S-H		N=O		HO-OH		C=O	
Molecular mass (g mol ⁻¹)	34.08		30.01		34.01		28.01	
Chemical reactivity	Very high		Very high		High		Moderate	
Toxicity concentration	5-30 µM		0.5-150 µM		0.5-500 µM		30-50 ppm	
Enzymatic production	Animals	Plants	Animals	Plants	Animals	Plants	Animals	Plants
	CBS CSE 3-MTS	L-/D-DES CAS CS SiR	eNOS iNOS nNOS	NRs NOS?	SOD POX	PAO SOD POX	HO-1	HO-1
Concentration in cells	nM-µM		nM		nM-µM		nM-µM	
Half life in vivo	Seconds-minutes		seconds		Seconds-minutes		Minutes	
Protein modification	Persulfidation		s-nitrosation		s-sulfenylation		?	

CBS: cystathionine β-synthase; CSE:Cystathionine γ-lyase; 3-MTS: 3-mercaptopyruvate sulfur transferase; L-/D-DES: cysteine desulphydrase; CAS: β-cyano-alanine synthase; CS:cysteine synthase; SiR: Sulfito reductasa; NOS: Nitric oxide synthase; NRs: Nitrate reductases; PAO: polyamine oxidase; SOD: Superoxide dismutase; POX: peroxidase; HO-1: Heme oxygenase 1.



The central idea of this presentation is that Romanian sulfurous balneary resources should not be understood only as historical or empirical spa factors. They can also be interpreted through the lens of contemporary H₂S biology. This does not mean that every effect of sulfurous waters can be reduced to a single molecule. Balneotherapy is always complex. It includes temperature, hydrostatic pressure, mineral composition, mechanical unloading, mud properties, microclimate, exercise, and neurovegetative responses. Nevertheless, H₂S provides a particularly strong mechanistic bridge between classical balneology and modern biomedical science.

Hydrogen sulfide (H₂S) - therapeutic relevance in rehabilitation and balneotherapy Systematic literature review and meta-analysis based on the PRISMA paradigm

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Abstract

Background. An active molecule in sulfurous mineral - medicinal waters and also in sapropelic mud is H₂S, a hormetic gaseous molecule that can actively penetrate the skin. While high levels of H₂S are extremely toxic, low levels are tolerated and have potential cytoprotective effects, with anti-inflammatory and antioxidant applications.

Objective. This systematic review aims to rigorously select related articles and identify within their content the main possible uses of hydrogen sulfide from balneary sources and to explain its physiological mechanisms and therapeutic properties.

Methods. To elaborate our systematic review, we have searched for relevant *open access* articles in 6 international databases: Cochrane¹, Elsevier¹, NCBI/PubMed¹, NCBI/PMC¹, PEDro¹, and ISI Web of Knowledge/Science¹, published from January 2016 until July 2021. The contextually quested keywords combinations/ syntaxes used are specified on this page. The eligible articles were analyzed in detail regarding pathologies addressed by hydrogen sulfide. All articles with any design (reviews, randomized controlled trials, non-randomized controlled trials, case-control studies, cross-sectional studies), if eligible according to the above-mentioned selection methodology, containing in the title the selected combinations, were included in the analysis. Articles were excluded in the second phase if they did not reach the relevance criterion.

Results. Our search identified, first, **291** articles. After eliminating the duplicates and non-ISI articles, remained **121** papers. In the second phase, we applied a PEDro selection filter, resulting in **108** articles that passed the relevance criterion and were included in this systematic review.

Conclusions. H₂S biology and medical relevance are not fully understood and used adequately for sanogenic or medical purposes. More research is needed to fully understand the mechanisms and importance of this therapeutic gas. The link between balneotherapy and medical rehabilitation regarding the usage of hydrogen sulfide emphasises the unity for this medical speciality.

Keywords: *Hydrogen sulfide / H₂S AND balneotherapy / inhalations / mud / Rheumatoid arthritis / neuroprotection / neurodegenerative disorders / Stroke / Parkinson / Alzheimer / Huntington / vascular dementia / Immune system / Diabetes / Cancer / Cardioprotection / Asthma / Allergic Rhinitis / COPD / COVID-19 / Burns / Analgesic effect / Clinical trials*

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Reviewers:

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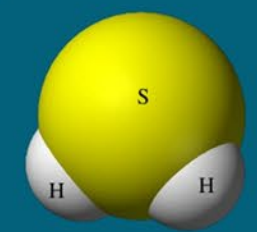


H₂S is, on the one hand, an **endogenous gas signal molecule**, which plays a vital role in various systems and diseases. On the other hand, H₂S is an **exogenous therapeutic gas**, found in combination with carbon dioxide in sulfurous waters, with medical properties well known and appreciated in balneotherapy, and also in **therapeutic muds**.

Hydrogen sulfide (H₂S) naturally occurs in volcanic gases, natural gas, and some therapeutic waters. Also, H₂S is produced when bacteria break down organic matter in the absence of oxygen.

→ What is Hydrogen Sulfide (H₂S)?

Hydrogen Sulfide Gas

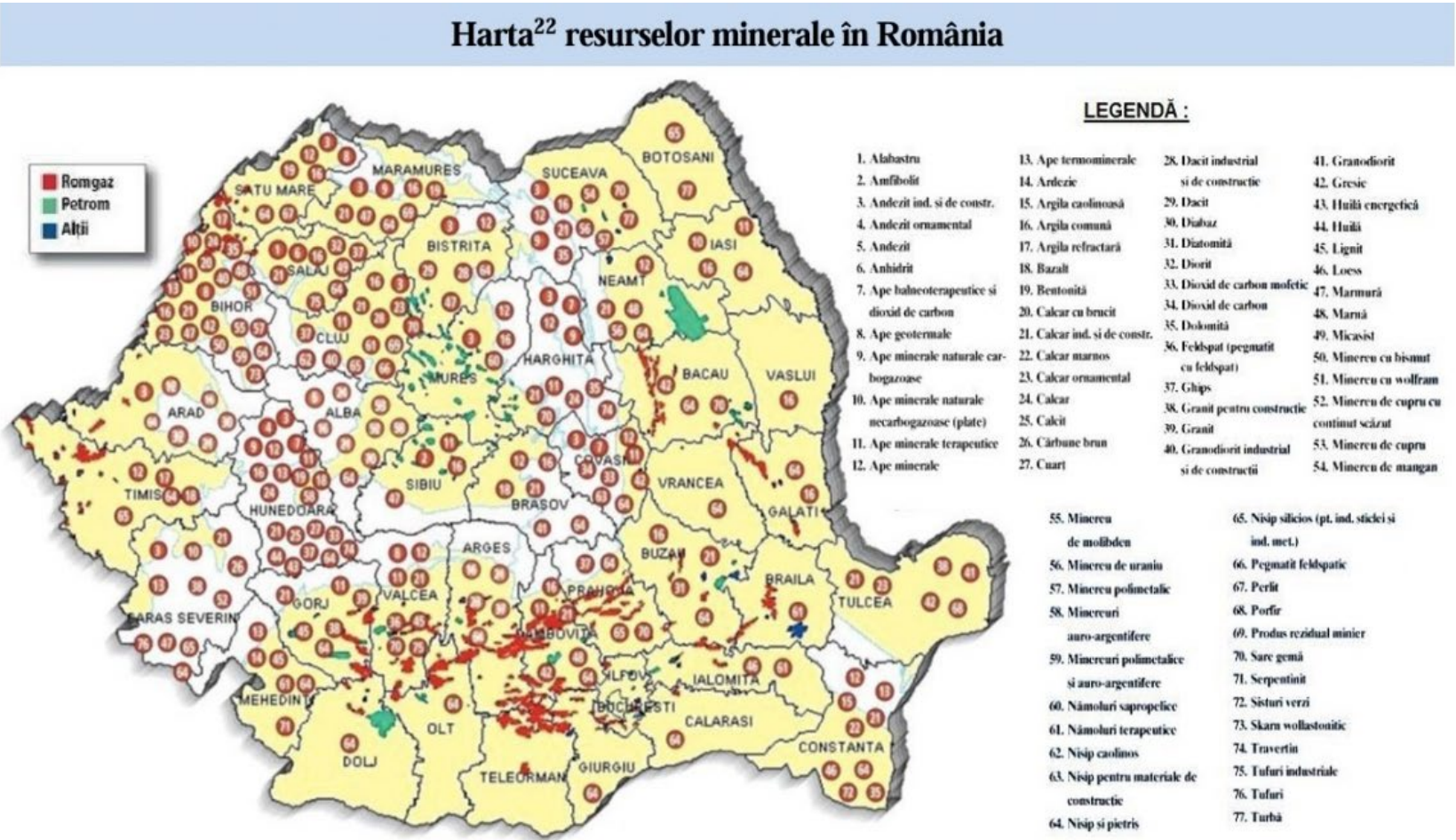
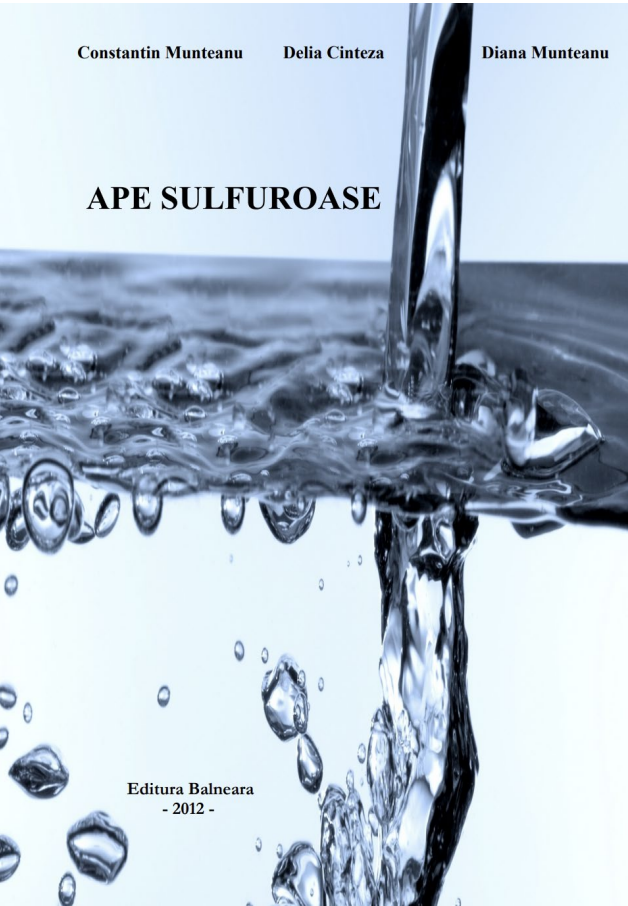


→ **Where do you find H₂S?**

→ **Properties of H₂S**

→ **How does H₂S affect individuals?**

Romania possesses a remarkable diversity of mineral waters, therapeutic lakes, peloids, and spa traditions. Among these, sulfurous waters occupy a distinct position. In classical balneological classification, sulfurous mineral waters are defined by the presence of reduced sulfur species such as hydrogen sulfide, hydrosulfide, sulfur, thiosulfate, and colloidal sulfur, often with a threshold of at least one milligram of titratable sulfur per liter. These waters are chemically heterogeneous. Some are simple sulfurous waters, but many are mixed waters, combining sulfurous characteristics with chlorosodic, carbonated, alkaline, calcium, magnesium, iodinated, or brominated profiles.



Romanian sulfurous resources are described in several classical and contemporary balneological sources. Important examples include Băile Herculane, Călimănești-Căciulata-Cozia, Băile Olănești, Băile Govora, Pucioasa, Mangalia, Săcelu, and Nicolina-iași. Other localities, such as Harghita Băi, Băile Boghiș, Venus, and related areas, are also mentioned in older balneological literature. The key point is that these are not interchangeable resources. Each source has its own hydrochemical profile, its own concentration of sulfur species, its own temperature, pH, mineralization, associated ions, and traditional indications.



Review

Recent Advances in Molecular Research on Hydrogen Sulfide (H₂S) Role in Diabetes Mellitus (DM)—A Systematic Review

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Citation: Munteanu, C.; Rotariu, M.; Turnea, M.; Dogaru, G.; Popescu, C.; Spinu, A.; Andone, I.; Postoiu, R.; Ionescu, E.V.; Oprea, C.; et al. Recent Advances in Molecular Research on Hydrogen Sulfide (H₂S) Role in Diabetes Mellitus (DM)—A Systematic Review. *Int. J. Mol. Sci.* **2022**, *23*, 6720. <https://doi.org/10.3390/ijms23126720>

Academic Editor: Alexandre Baykov

Received: 27 May 2022

Accepted: 13 June 2022

Published: 16 June 2022

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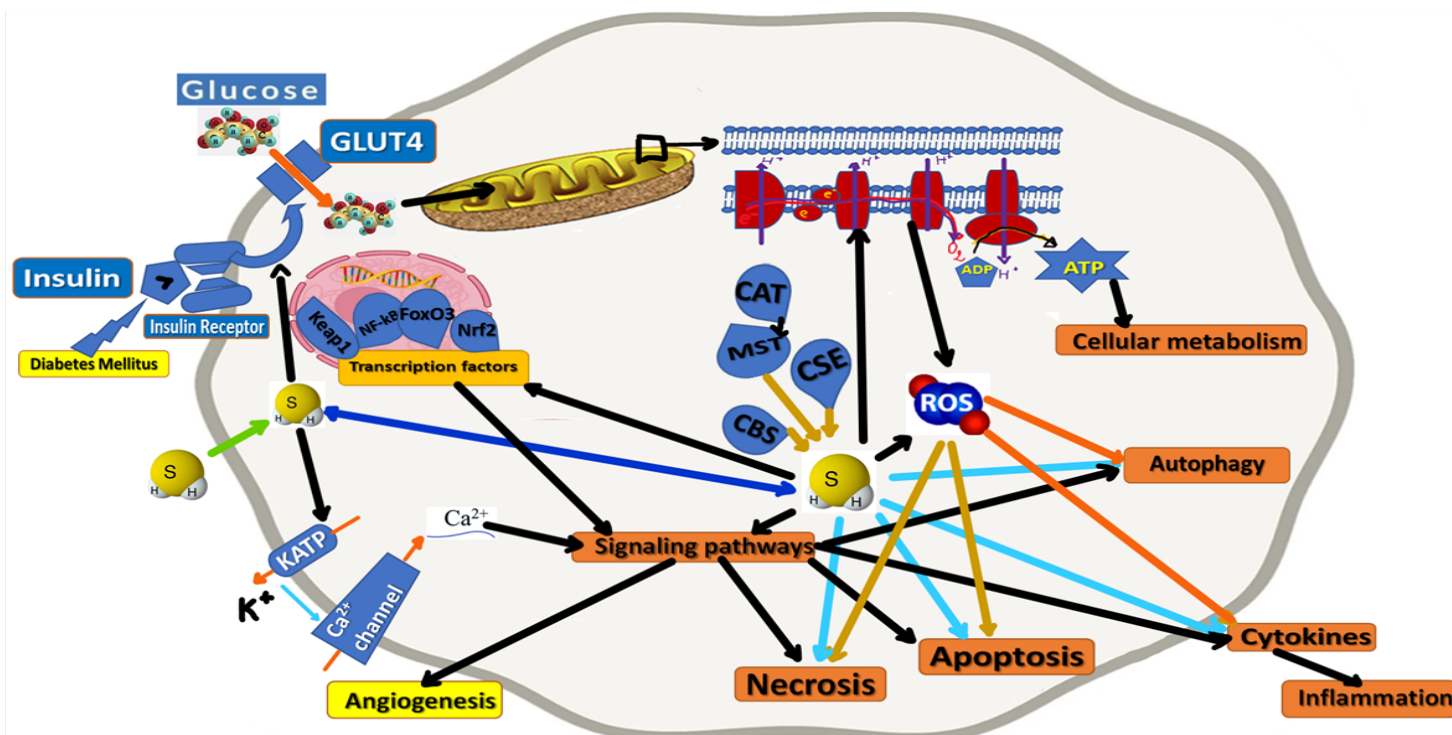
Abstract: Abundant experimental data suggest that hydrogen sulfide (H₂S) is related to the pathophysiology of Diabetes Mellitus (DM). Multiple molecular mechanisms, including receptors, membrane ion channels, signaling molecules, enzymes, and transcription factors, are known to be responsible for the H₂S biological actions; however, H₂S is not fully documented as a gaseous signaling molecule interfering with DM and vascular-linked pathology. In recent decades, multiple approaches regarding therapeutic exploitation of H₂S have been identified, either based on H₂S exogenous apport or on its modulated endogenous biosynthesis. This paper aims to synthesize and systematize, as comprehensively as possible, the recent literature-related data regarding the therapeutic/rehabilitative role of H₂S in DM. This review was conducted following the “Preferred reporting items for systematic reviews and meta-analyses” (PRISMA) methodology, interrogating five international medically renowned databases by specific keyword combinations/“syntaxes” used contextually, over the last five years (2017–2021). The respective search/filtered and selection methodology we applied has identified, in the first step, 212 articles. After deploying the next specific quest steps, 51 unique published papers qualified for minute analysis resulted. To these bibliographic resources obtained through the PRISMA methodology, in order to have the best available information coverage, we added 86 papers that were freely found by a direct internet search. Finally, we selected for a connected meta-analysis eight relevant reports that included 1237 human subjects elicited from clinical trial registration platforms. Numerous H₂S releasing/stimulating compounds have been produced, some being used in experimental models. However, very few of them were further advanced in clinical studies, indicating that the development of H₂S as a therapeutic agent is still at the beginning.

Keywords: hydrogen sulfide (H₂S); Diabetes Mellitus (DM); DM vascular-linked pathology; systematic review; oxidative phosphorylation; ROS (Reactive Oxygen Species)

1. Introduction

Diabetes Mellitus (DM) is a non-communicable chronic metabolic disease [1] characterized by prolonged hyperglycemia. Type 1 DM is a chronic condition in which the body's pancreatic β cells, determined by different causes, reduce insulin production. Instead, type

This heterogeneity is scientifically important. It means that “sulfurous water” should not be treated as a single therapeutic category. From a modern perspective, each Romanian H₂S-related resource should be profiled by its chemical fingerprint: total sulfide, free H₂S, hydrosulfide ions, thiosulfate, sulfate, polysulfides, pH, redox potential, temperature, dissolved oxygen, total dissolved solids, salinity, hardness, and associated trace elements. Pucioasa, for example, has been investigated as a sulfurous balneotherapeutic area, with studies assessing physicochemical parameters and metal concentrations in spring waters. This type of analytical work is precisely the direction needed for the modernization of balneology.



Intimate mechanisms as molecular therapeutic/rehabilitative targets of H₂S in the case of cells influenced by DM (which impacts glucose uptake, affecting the relation of insulin signal trans-mission pathway with the cell glucose uptake). Intimate connections are indicated through black arrows, while increasing influences are marked by green arrows and inhibiting or reducing im-pacts of H₂S through blue arrows. Finally, the biosynthesis pathways are stated, represented by cystathionin- β -synthase (CBS), cystathionin- γ -lyase (CSE), and 3-mercaptopyruvate sulfurtrans-ferase (MST), the latter connected with cysteine aminotransferase (CAT).

Physiological properties of Hydrogen sulfide (H_2S)

Authors	Ref. no.	Subject - data
(Sun, 2021)	(3)	An Updated Insight Into Molecular Mechanism of H_2S in Cardiomyopathy
(Ciccone, 2021)	(12)	Endothelium as a Source and Target of H_2S to Improve Its Trophism and Function
(Liu, 2018)	(31)	H_2S attenuates myocardial fibrosis through the JAK/STAT signaling pathway
(Kar, 2019)	(33)	H_2S -mediated regulation of cell death signaling ameliorates adverse cardiac remodeling
(Dominic, 2021)	(26)	Decreased availability of nitric oxide and H_2S is a hallmark of COVID-19
(Yang, 2019)	(30)	Exogenous H_2S mitigates myocardial fibrosis through suppression of Wnt pathway
(Sun, 2019)	(38)	Exogenous H_2S reduces the acetylation levels of mitochondrial respiratory enzymes
(Zou, 2017)	(9)	H_2S ameliorates cognitive dysfunction in streptozotocin-induced diabetic rats
(Zhao, 2021)	(50)	H_2S Plays an Important Role in Diabetic Cardiomyopathy
(Luo, 2019)	(28)	H_2S upregulates renal AQP-2 protein expression and promotes urine concentration
(Roa-Coria, 2019)	(42)	Possible involvement of peripheral TRP channels in the H_2S -induced hyperalgesia
(George, 2018)	(7)	Treating inflammation and oxidative stress with H_2S during age-related macular degeneration
(Qiu, 2018)	(55)	Alpha-lipoic acid regulates the autophagy of vascular smooth muscle cells elevating H_2S level
(Hu, 2017)	(24)	Chelerythrine Attenuates Renal Ischemia/ Reperfusion-induced Myocardial Injury
(Wu, 2017)	(15)	Exogenous H_2S facilitating ubiquitin aggregates clearance via autophagy
(Yu, 2020)	(75)	Exogenous H_2S Induces Hrd1 S-sulfhydration and Prevents CD36 Translocation via VAMP3
(Yang, 2017)	(49)	Exogenous H_2S regulates endoplasmic reticulum-mitochondria crosstalk to inhibit apoptosis
(Ma, 2017)	(89)	Exogenous H_2S Ameliorates Diabetes-Associated Cognitive Decline
(Kar, 2019)	(34)	H_2S Ameliorates Homocysteine-Induced Cardiac Remodeling and Dysfunction
(Jiang, 2020)	(37)	H_2S Ameliorates Lung Ischemia-Reperfusion Injury Through SIRT1 Signaling Pathway
(Loiselle, 2020)	(87)	H_2S and hepatic lipid metabolism - a critical pairing for liver health
(Wu, 2019)	(36)	H_2S Inhibits High Glucose-Induced Neuronal Senescence by Improving Autophagic Flux
(Li, 2017)	(68)	H_2S reduced renal tissue fibrosis by regulating autophagy in diabetic rats
(Testai, 2021)	(11)	Modulation of EndMT by H_2S in the Prevention of Cardiovascular Fibrosis
(Cheng, 2020)	(10)	Potential role of H_2S in diabetes-impaired angiogenesis and ischemic tissue repair
(Tabassum, 2020)	(18)	Protective effect of H_2S on oxidative stress-induced neurodegenerative diseases
(Liu, 2017)	(52)	H_2S modulating mitochondrial morphology to promote mitophagy in endothelial cells

Pathophysiological properties of H_2S

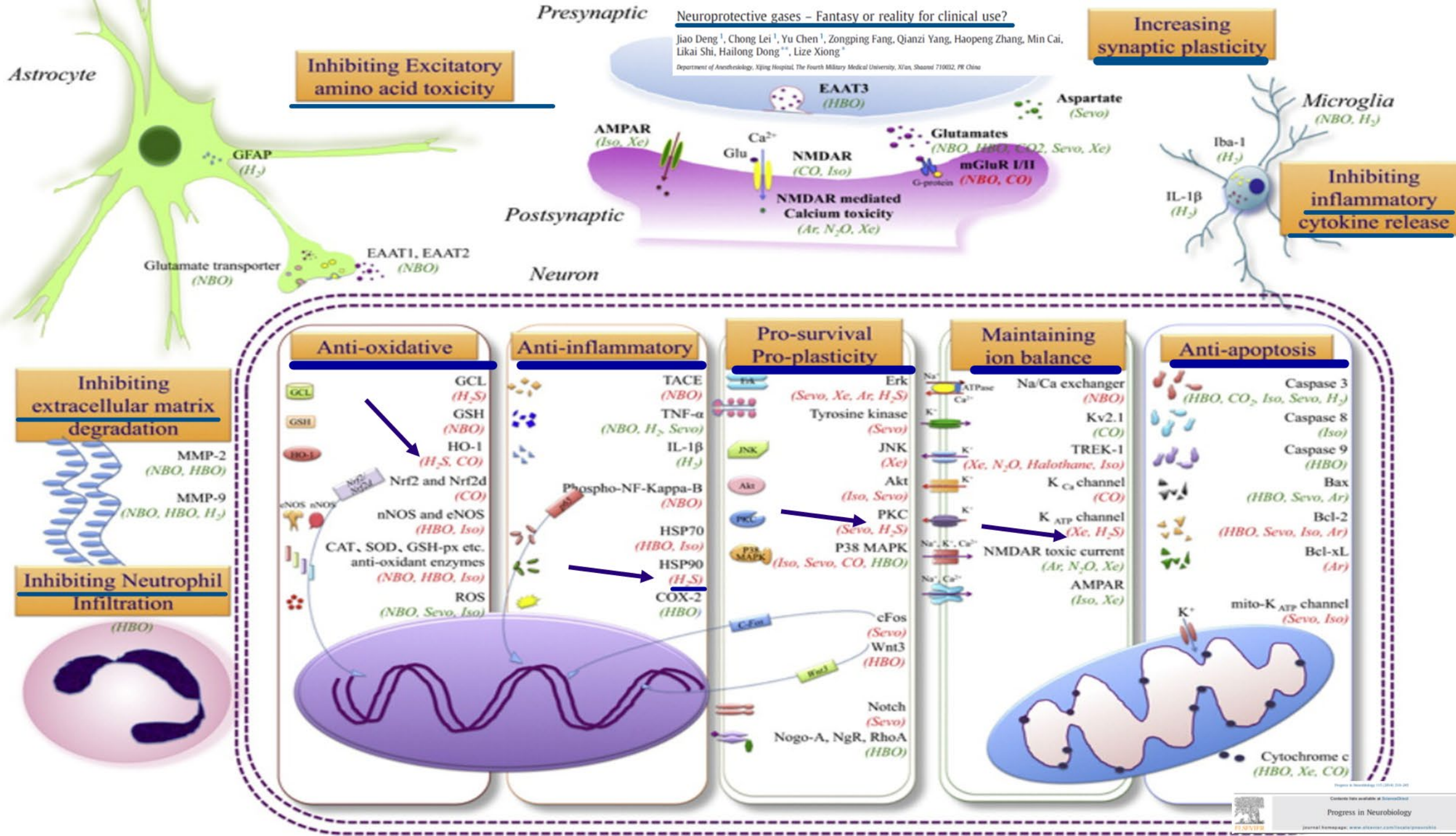
Authors	Ref. no.	Subject - data
(Citi, 2021)	(8)	Role of H_2S in endothelial dysfunction: Pathophysiology and therapeutic approaches
(Sun, 2019)	(21)	H_2S and Subsequent Liver Injury
(Kang, 2020)	(20)	H_2S as a Potential Alternative for the Treatment of Myocardial Fibrosis
(Szabo, 2017)	(27)	Pharmacological Modulation of H_2S Levels
(Sun, 2020)	(95)	The Link Between Inflammation and H_2S
(Kar, 2019)	(102)	Exercise Training Promotes Cardiac H_2S Biosynthesis and Mitigates Pyroptosis
(Zheng, 2020)	(97)	H_2S protects against diabetes-accelerated atherosclerosis by preventing the activation of NLRP3
(Li, 2019)	(103)	Exogenous H_2S protects against high glucose-induced apoptosis and oxidative stress
(Li, 2017)	(100)	H_2S improves renal fibrosis in STZ-induced diabetic rats by ameliorating TGF-beta 1 expression
(Jia, 2020)	(99)	H_2S mitigates myocardial inflammation by inhibiting nucleotide-binding oligomerization domain-like receptor protein 3 inflammasome activation in diabetic rats

H_2S – role in DM and associated vascular pathology

Authors	Ref. no.	Subject - data
(Zhang, 2021)	(65)	H_2S regulates insulin secretion and insulin resistance in diabetes mellitus
(Suzuki, 2017)	(110)	Clinical Implication of Plasma H_2S Levels in Japanese Patients with Type 2 Diabetes
(Gheibi, 2020)	(5)	Regulation of carbohydrate metabolism by NO and H_2S : Implications in diabetes
(Zhou, 2019)	(113)	H_2S Prevents Elastin Loss and Attenuates Calcification Induced by High Glucose
(Comas, 2021)	(109)	The Impact of H_2S on Obesity-Associated Metabolic Disturbances
(Gheibi, 2019)	(107)	Effects of H_2S on Carbohydrate Metabolism in Obese Type 2 Diabetic Rats
(Chen, 2021)	(106)	Role of H_2S in the Endocrine System
(Luo, 2017)	(108)	The Role of Exogenous H_2S in Free Fatty Acids Induced Inflammation in Macrophages

Exo/endogenous sources of therapeutic H_2S in DM

Authors	Ref. no.	Subject - data
(Melino, 2019)	(2)	Natural H_2S Donors from Allium sp. as a Nutraceutical Approach in Type 2 Diabetes
(Yang, 2017)	(25)	H_2S Releasing/ Stimulating Reagents
(John, 2017)	(22)	GY4137, a H_2S Donor Modulates miR194-Dependent Collagen Realignment
(Bitar, 2018)	(70)	H_2S Donor NaHS Improves Metabolism and Reduces Muscle Atrophy in Type 2 Diabetes
(John, 2019)	(6)	H_2S inhibits Ca^{2+} -induced mitochondrial permeability transition pore opening
(Ding, 2017)	(137)	High Glucose Induces Mouse Mesangial Cell Overproliferation via Inhibition of H_2S Synthesis





Review

Cellular and Molecular Targets for Non-Invasive, Non-Pharmacological Therapeutic/Rehabilitative Interventions in Acute Ischemic Stroke

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Citation: Onose, G.; Anghelescu, A.; Blendea, D.; Ciobanu, V.; Daia, C.; Firan, F.C.; Oprea, M.; Spinu, A.; Popescu, C.; Ionescu, A.; et al. Cellular and Molecular Targets for Non-Invasive, Non-Pharmacological Therapeutic/Rehabilitative Interventions in Acute Ischemic Stroke. *Int. J. Mol. Sci.* **2022**, *23*, 907. <https://doi.org/10.3390/ijms23020907>

Academic Editor: Peter Kraft

Received: 17 December 2021

Accepted: 12 January 2022

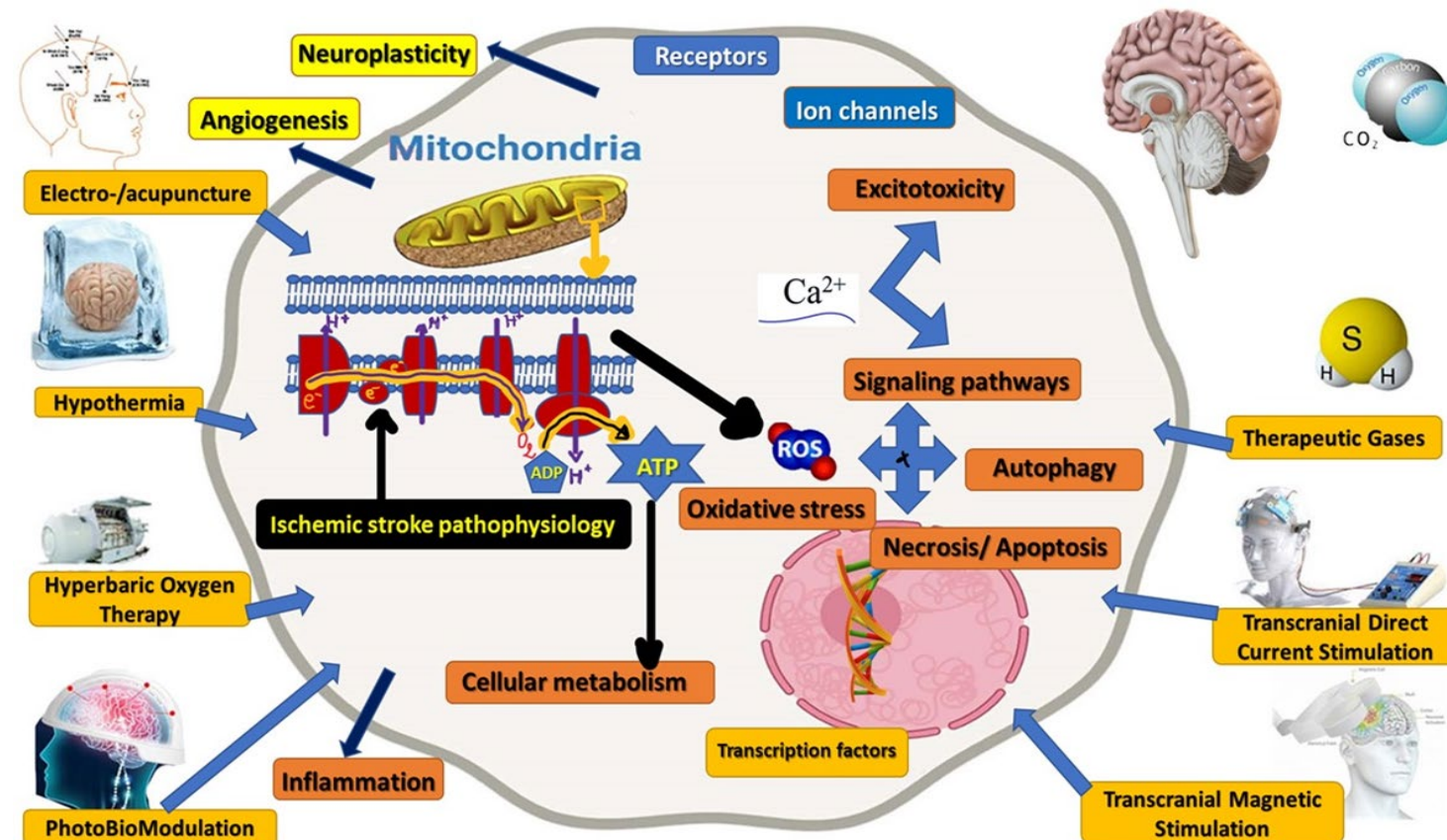
Published: 14 January 2022

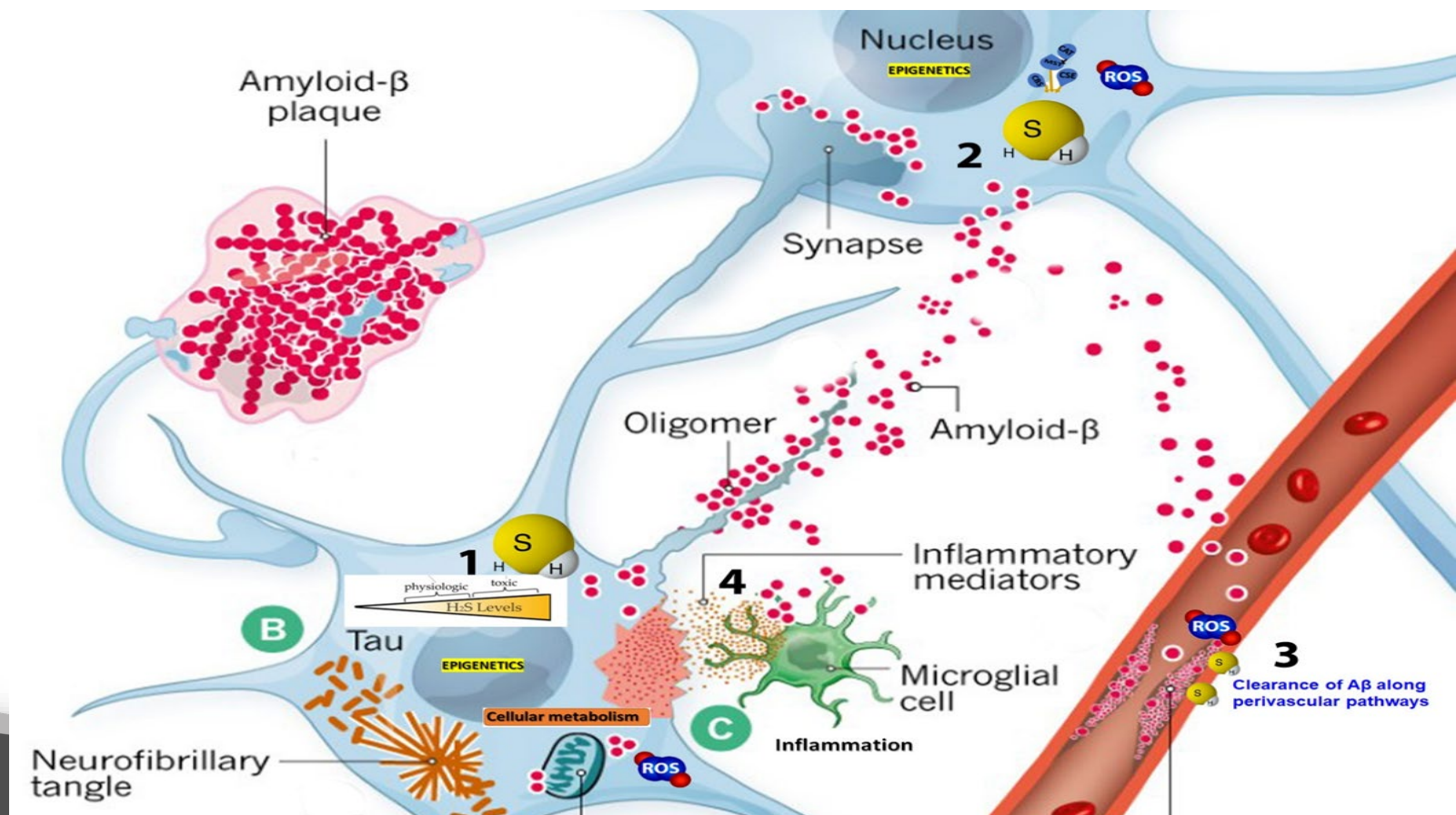
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Abstract: BACKGROUND: Cerebral circulation delivers the blood flow to the brain through a dedicated network of sanguine vessels. A healthy human brain can regulate cerebral blood flow (CBF) according to any physiological or pathological challenges. The brain is protected by its self-regulatory mechanisms, which are dependent on neuronal and support cellular populations, including endothelial ones, as well as metabolic, and even myogenic factors. OBJECTIVES: Accumulating data suggest that "non-pharmacological" approaches might provide new opportunities for stroke therapy, such as electro-/acupuncture, hyperbaric oxygen therapy, hypothermia/cooling, photobiomodulation, therapeutic gases, transcranial direct current stimulations, or transcranial magnetic stimulations. We reviewed the recent data on the mechanisms and clinical implications of these non-pharmaceutical treatments. METHODS: To present the state-of-the-art for currently available non-invasive, non-pharmacological-related interventions in acute ischemic stroke, we accomplished this synthetic and systematic literature review based on the Preferred Reporting Items for Systematic Principles Reviews and Meta-Analyses (PRISMA). RESULTS: The initial number of obtained articles was 313. After fulfilling the five steps in the filtering/selection methodology, 54 fully eligible papers were selected for synthetic review. We enhanced our documentation with other bibliographic resources connected to our subject, identified in the literature within a non-standardized search, to fill the knowledge gaps. Fifteen clinical trials were also identified. DISCUSSION: Non-invasive, non-pharmacological therapeutic/rehabilitative interventions for acute ischemic stroke are mainly holistic therapies. Therefore, most of them are not yet routinely used in clinical practice, despite some possible beneficial effects, which have not been systematically proven in more related studies. Moreover, four of the identified

A critical concept here is dose-dependent duality. H₂S is neither simply beneficial nor simply harmful. At high concentrations, it is toxic and potentially lethal. At low physiological or therapeutic concentrations, it may regulate signaling pathways that protect tissues from oxidative stress, inflammation, apoptosis, and metabolic dysfunction. This is essentially a hormetic model: the biological effect depends on concentration, exposure route, duration, tissue context, and the redox state of the organism. For balneology, this is not a theoretical detail. It means that source characterization, medical supervision, and standardized protocols are essential.







The Role of Hydrogen Sulfide (H₂S) in Epigenetic Regulation of Neurodegenerative Diseases: A Systematic Review

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Abstract: This review explores the emerging role of hydrogen sulfide (H₂S) in modulating epigenetic mechanisms involved in neurodegenerative diseases. Accumulating evidence has begun to elucidate the multifaceted ways in which H₂S influences the epigenetic landscape and, subsequently, the progression of various neurodegenerative disorders, including Alzheimer's, Parkinson's, and Huntington's disease. H₂S can modulate key components of the epigenetic machinery, such as DNA methylation, histone modifications, and non-coding RNAs, impacting gene expression and cellular functions relevant to neuronal survival, inflammation, and synaptic plasticity. We synthesize recent research that positions H₂S as an essential player within this intricate network, with the potential to open new therapeutic avenues for these currently incurable conditions. Despite significant progress, there remains a considerable gap in our understanding of the precise molecular mechanisms and the potential therapeutic implications of modulating H₂S levels or its downstream targets. We conclude by identifying future directions for research aimed at exploiting the therapeutic potential of H₂S in neurodegenerative diseases.

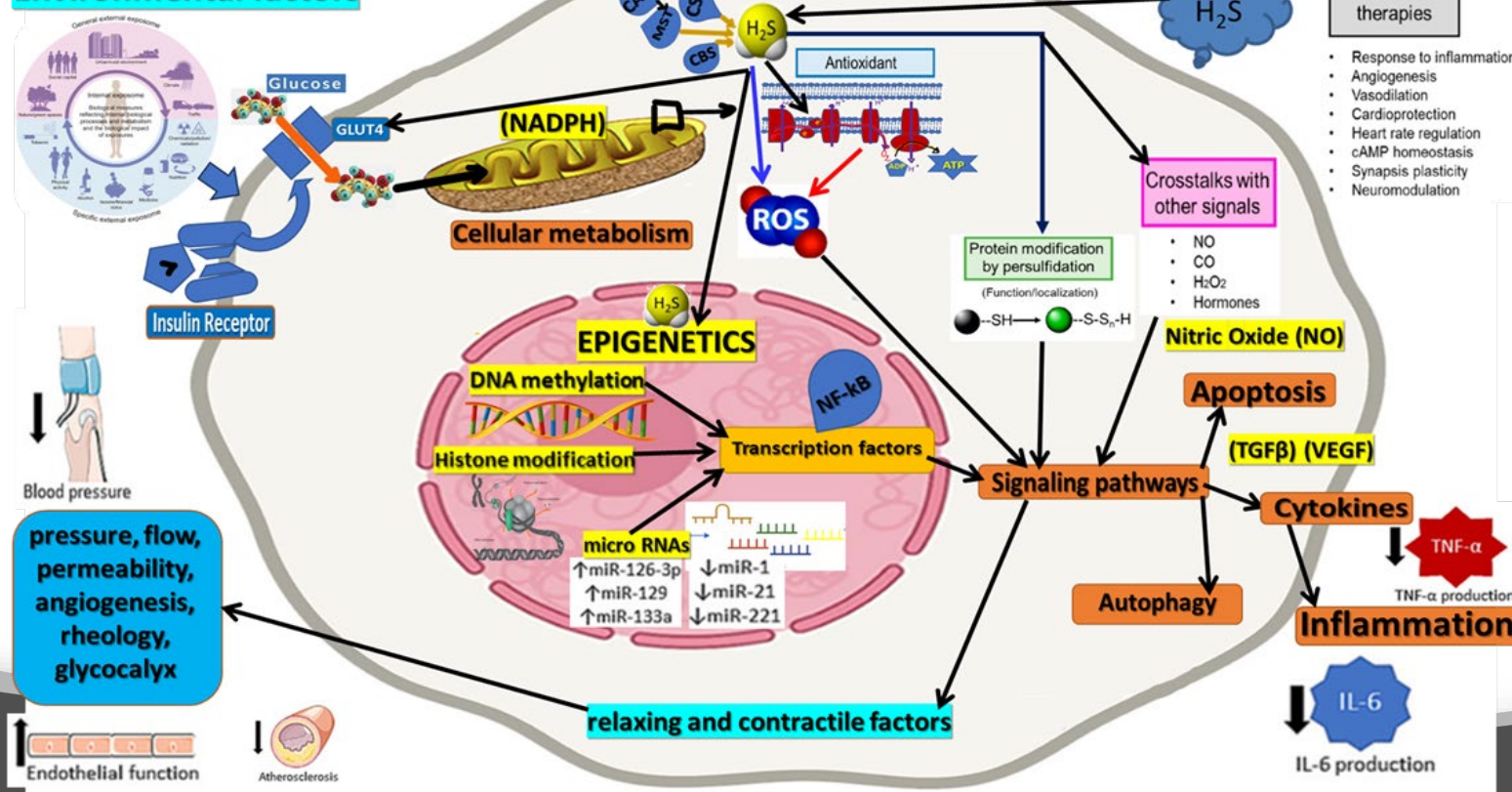
Keywords: hydrogen sulfide; epigenetic regulation; neurodegenerative diseases; DNA methylation; Histone modifications; non-coding RNAs; Alzheimer's disease; Parkinson's disease; Huntington's disease

1. Introduction

Neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's, pose a formidable challenge in modern medicine [1,2]. These conditions are characterized by the relentless and irreversible loss of neurons, leading to a gradual decline in cognitive and motor functions [3]. They have become a significant subset of non-communicable diseases, exacerbated by our longer human lifespan [4], impacting the lives of millions of individuals worldwide. Not only do these diseases cause emotional distress, but they also impose substantial economic burdens on society [5].

The nervous system is another area of major interest. H₂S is produced in the brain, participates in neuromodulation, and may influence synaptic plasticity, NMDA receptor signaling, calcium homeostasis, mitochondrial function, neuroinflammation, and antioxidant defense. The presentation includes slides on Alzheimer's disease, neurodegeneration, synaptic plasticity, and the microbiota-gut-brain axis. These are not yet direct indications for sulfurous spa therapy in a strong evidence-based sense. Rather, they show that H₂S biology belongs to the same mechanistic universe as modern neurorehabilitation: neuroplasticity, inflammation resolution, mitochondrial health, vascular regulation, and systemic homeostasis.

Environmental factors



Topical Reappraisal of Molecular Pharmacological Approaches to Endothelial Dysfunction in Diabetes Mellitus Angiopathy

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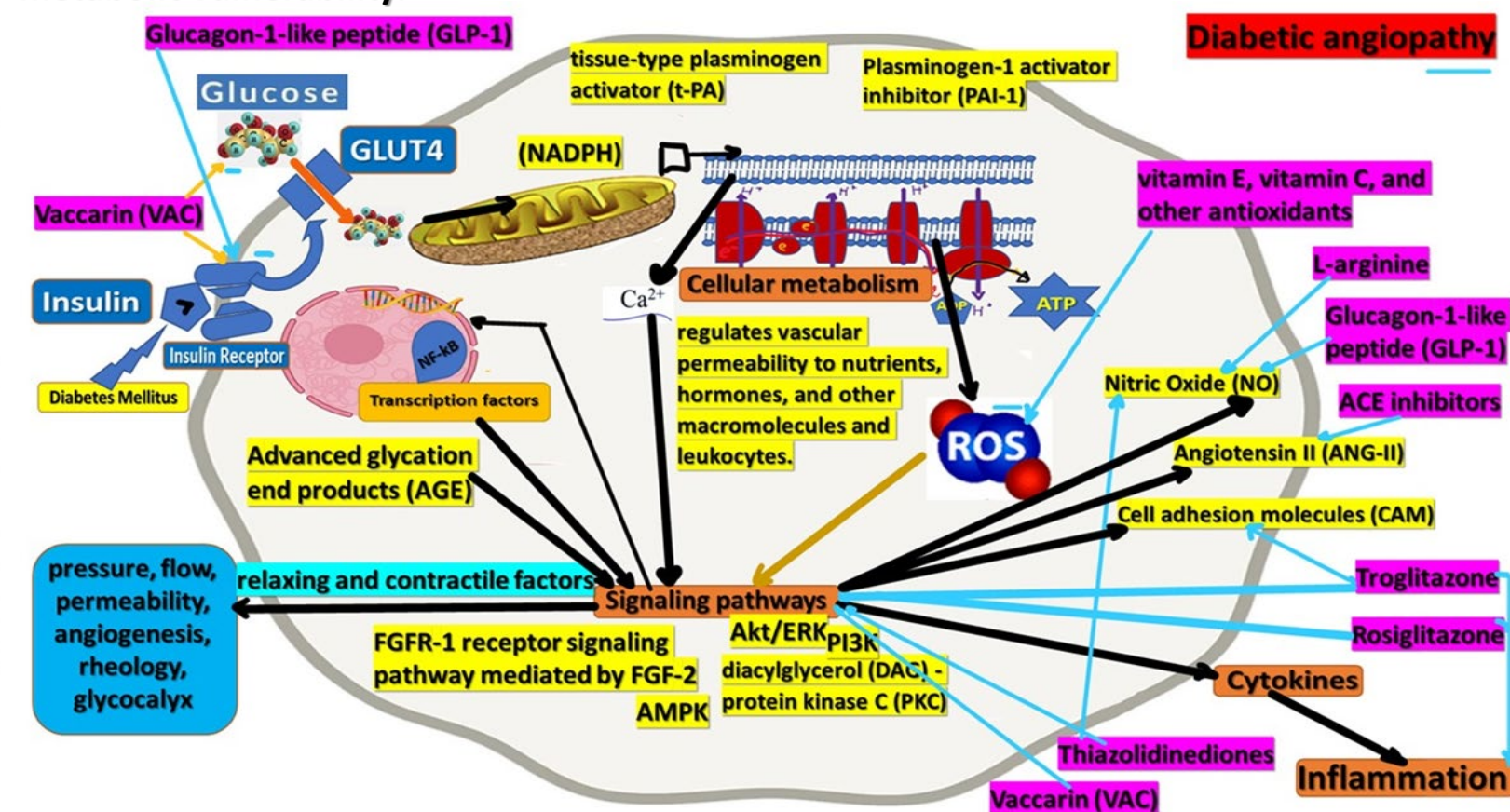
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Abstract: Diabetes mellitus (DM) is a frequent medical problem, affecting more than 4% of the population in most countries. In the context of diabetes, the vascular endothelium can play a crucial pathophysiological role. If a healthy endothelium—which is a dynamic endocrine organ with autocrine and paracrine activity—regulates vascular tone and permeability and assures a proper balance between coagulation and fibrinolysis, and vasodilation and vasoconstriction, then, in contrast, a dysfunctional endothelium has received increasing attention as a potential contributor to the pathogenesis of vascular disease in diabetes. Hyperglycemia is indicated to be the major causative factor in the development of endothelial dysfunction. Furthermore, many shreds of evidence suggest that the progression of insulin resistance in type 2 diabetes is parallel to the advancement of endothelial dysfunction in atherosclerosis. To present the state-of-the-art data regarding endothelial dysfunction in diabetic micro- and macroangiopathy, we constructed this literature review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We interrogated five medical databases: Elsevier, PubMed, PMC, PEDro, and ISI Web of Science.

Keywords: diabetes mellitus; endothelial dysfunction; microangiopathy; macroangiopathy

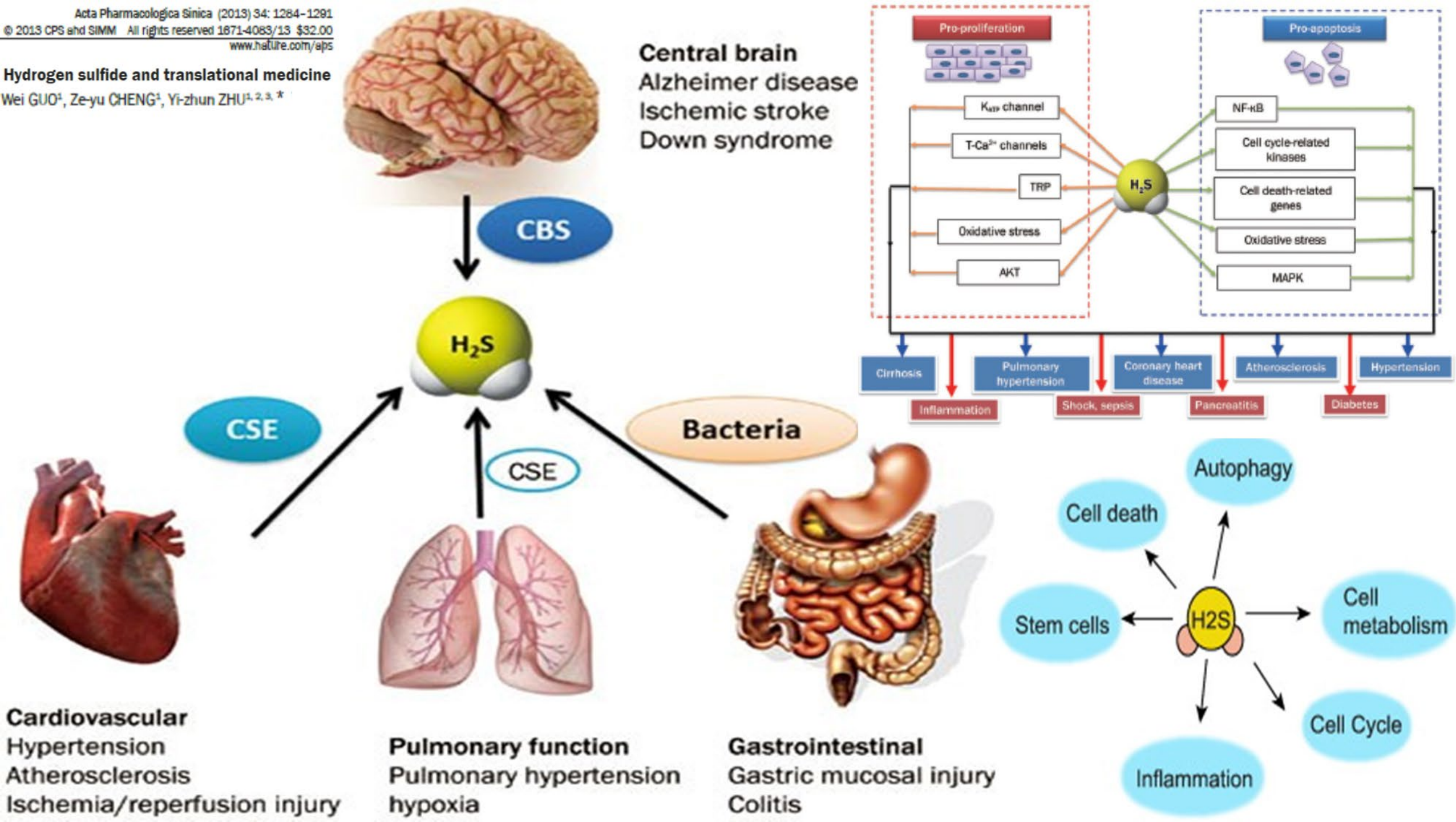


Diabetes mellitus is associated with oxidative stress, chronic low-grade inflammation, endothelial dysfunction, impaired nitric oxide signaling, mitochondrial stress, altered glucose uptake, and vascular remodeling. H₂S has been studied in relation to insulin signaling, GLUT4 translocation, mitochondrial function, inflammatory cytokines, angiogenesis, and endothelial barrier function. For Romanian balneology, this is clinically relevant because many spa patients are elderly, metabolically complex, and affected by multimorbidity. Sulfurous resources may therefore be integrated into rehabilitation models addressing not only the joint or the skin, but also systemic vascular and metabolic vulnerability.



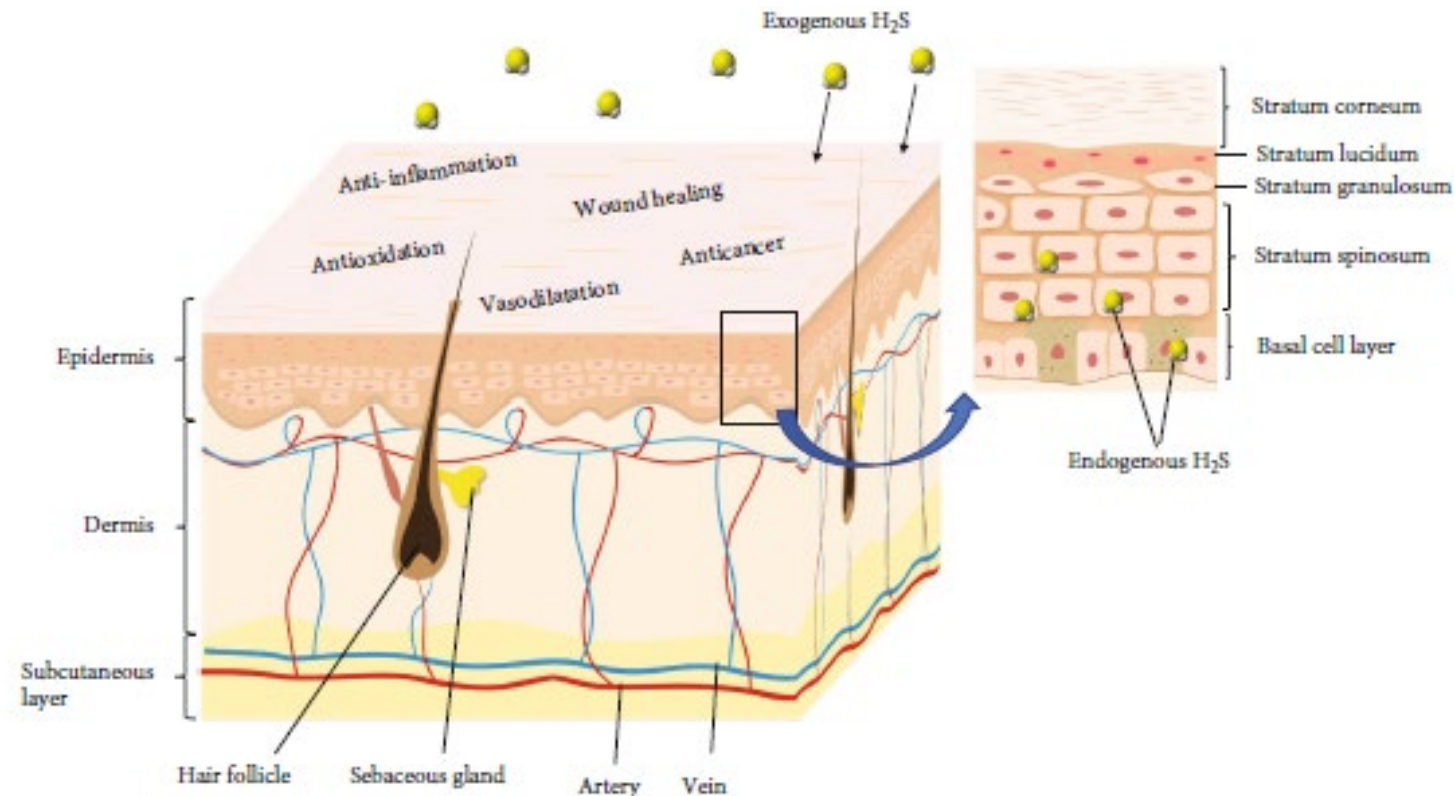
Hydrogen sulfide and translational medicine

Wei GUO¹, Ze-yu CHENG¹, Yi-zhun ZHU^{1, 2, 3, *}



The skin is another essential interface. In sulfurous baths, H_2S and related sulfur species interact first with the epidermis, dermis, cutaneous vessels, nerve endings, sebaceous glands, immune cells, and connective tissue. The slide on skin structure illustrates the importance of this local exposure. The classical use of sulfurous waters in dermatology, including selected chronic inflammatory or keratinization disorders, may be linked to local vasodilation, modulation of inflammation, antimicrobial effects, keratolytic actions, and changes in redox signaling. Older balneological literature also describes absorption routes through the skin, digestive tract, respiratory mucosa, and other mucosal surfaces, which is relevant for baths, drinking cures, inhalations, and local applications.

In water and in biological systems, sulfur does not exist in only one form. H_2S , HS^- , persulfides, polysulfides, thiosulfate, sulfite, sulfate, and protein-bound sulfane sulfur form a dynamic redox network. The therapeutic identity of a sulfurous spring therefore depends not only on the nominal presence of H_2S , but on the entire sulfur speciation profile. This has implications for storage, transport, bottling, bath preparation, inhalation procedures, and mud maturation. Sulfurous waters are chemically alive systems, and they change with oxygen exposure, temperature, microbial activity, and time.



Review

Signaling Paradigms of H₂S-Induced Vasodilation:
A Comprehensive Review

Constantin Munteanu ^{1,2,*}, Cristina Popescu ^{2,3,*}, Andreea-Iulia Vlădulescu-Trandafir ^{2,3} and Gelu Onose ^{2,3}

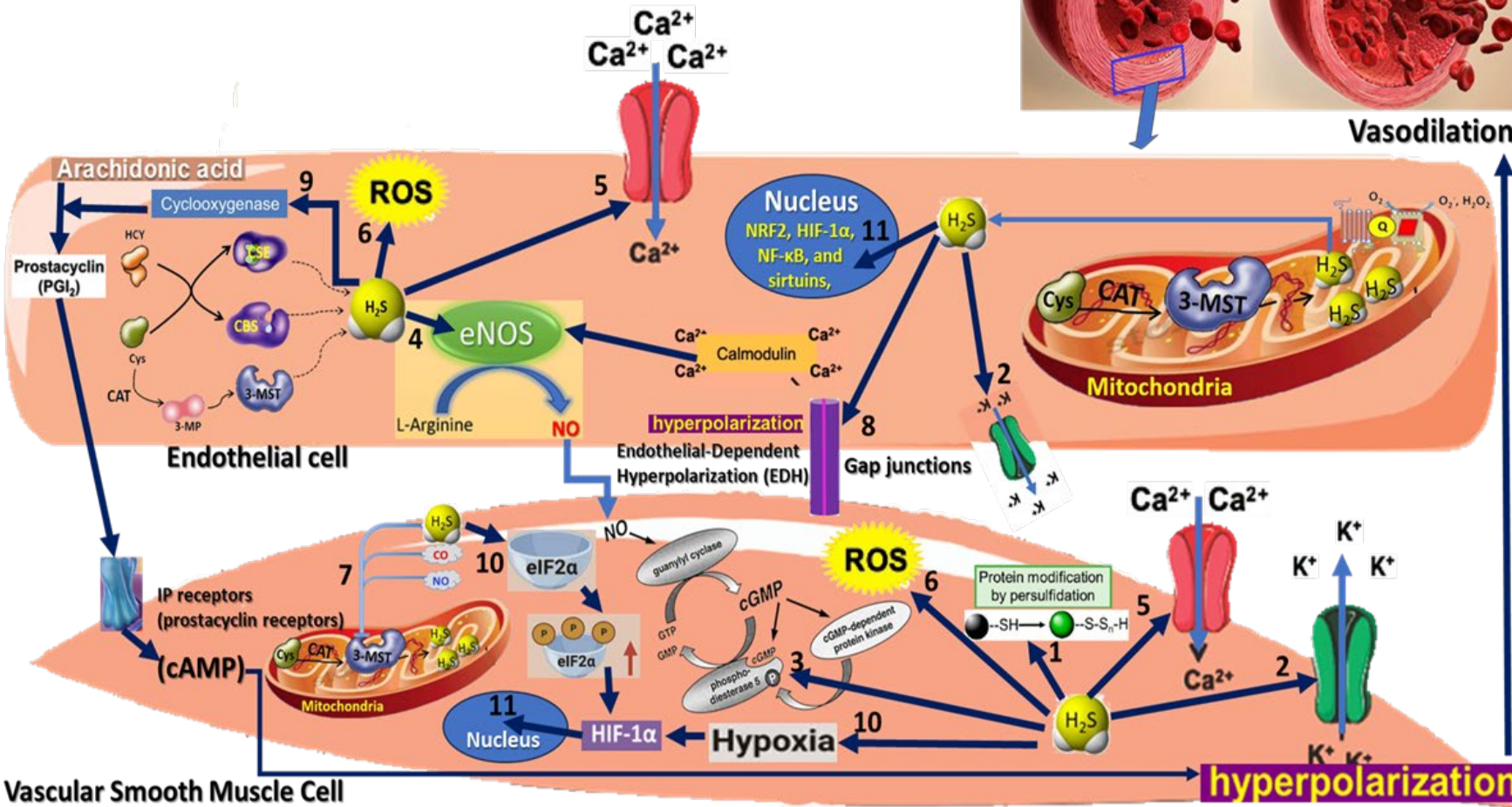
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Abstract: Hydrogen sulfide (H₂S), a gas traditionally considered toxic, is now recognized as a vital endogenous signaling molecule with a complex physiology. This comprehensive study encompasses a systematic literature review that explores the intricate mechanisms underlying H₂S-induced vasodilation. The vasodilatory effects of H₂S are primarily mediated by activating ATP-sensitive potassium (K_{ATP}) channels, leading to membrane hyperpolarization and subsequent relaxation of vascular smooth muscle cells (VSMCs). Additionally, H₂S inhibits L-type calcium channels, reducing calcium influx and diminishing VSMC contraction. Beyond ion channel modulation, H₂S profoundly impacts cyclic nucleotide signaling pathways. It stimulates soluble guanylyl cyclase (sGC), increasing the production of cyclic guanosine monophosphate (cGMP). Elevated cGMP levels activate protein kinase G (PKG), which phosphorylates downstream targets like vasodilator-stimulated phosphoprotein (VASP) and promotes smooth muscle relaxation. The synergy between H₂S and nitric oxide (NO) signaling further amplifies vasodilation. H₂S enhances NO bioavailability by inhibiting its degradation and stimulating endothelial nitric oxide synthase (eNOS) activity, increasing cGMP levels and potent vasodilatory responses. Protein sulphydration, a post-translational modification, plays a crucial role in cell signaling. H₂S-sulfurates oxidized cysteine residues, while polysulfides (H₂Sn) are responsible for S-sulfurating reduced cysteine residues. Sulphydration of key proteins like K_{ATP} channels and sGC enhances their activity, contributing to the overall vasodilatory effect. Furthermore, H₂S interaction with endothelium-derived hyperpolarizing factor (EDHF) pathways adds another layer to its vasodilatory mechanism. By enhancing EDHF activity, H₂S facilitates the hyperpolarization and relaxation of VSMCs through gap junctions between endothelial cells and VSMCs. Recent findings suggest that H₂S can also modulate transient receptor potential (TRP) channels, particularly TRPV4 channels, in endothelial cells. Activating these channels by H₂S promotes calcium entry, stimulating the production of vasodilatory agents like NO and prostacyclin, thereby regulating vascular tone. The comprehensive understanding of H₂S-induced vasodilation mechanisms highlights its therapeutic potential. The multifaceted approach of H₂S in modulating vascular tone presents a promising strategy for developing novel treatments for hypertension, ischemic conditions, and other vascular disorders. The interaction of H₂S with ion channels, cyclic nucleotide signaling, NO pathways, ROS (Reactive Oxygen Species) scavenging, protein sulphydration, and EDHF underscores its complexity and therapeutic relevance. In conclusion, the intricate signaling paradigms of H₂S-induced vasodilation offer valuable insights into its physiological role and therapeutic potential, promising innovative approaches for managing various vascular diseases through the modulation of vascular tone.

Keywords: hydrogen sulfide (H₂S); vasodilation; protein sulphydration; ROS scavenging; endothelial function

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H₂S Signaling Paradigms in Vasodilation



Hydrogen Sulfide and Oxygen Homeostasis in Atherosclerosis: A Systematic Review from Molecular Biology to Therapeutic Perspectives

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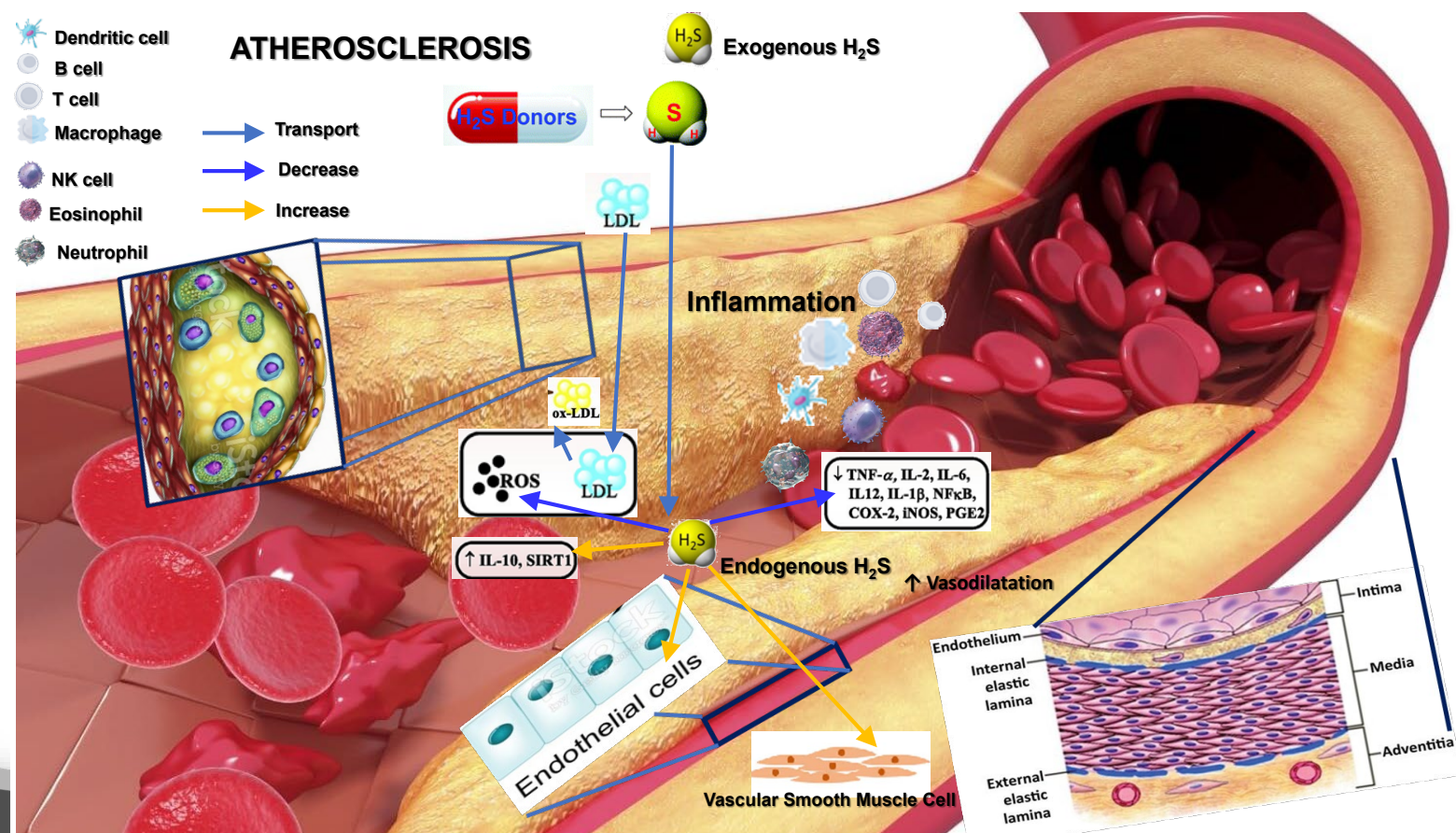
Abstract: Atherosclerosis is a complex pathological condition marked by the accumulation of lipids in the arterial wall, leading to the development of plaques that can eventually rupture and cause thrombotic events. In recent years, hydrogen sulfide (H₂S) has emerged as a key mediator of cardiovascular homeostasis, with potential therapeutic applications in atherosclerosis. This systematic review highlights the importance of understanding the complex interplay between H₂S, oxygen homeostasis, and atherosclerosis and suggests that targeting H₂S signaling pathways may offer new avenues for treating and preventing this condition. Oxygen homeostasis is a critical aspect of cardiovascular health, and disruption of this balance can contribute to the development and progression of atherosclerosis. Recent studies have demonstrated that H₂S plays an important role in maintaining oxygen homeostasis by regulating the function of oxygen-sensing enzymes and transcription factors in vascular cells. H₂S has been shown to modulate endothelial nitric oxide synthase (eNOS) activity, which plays a key role in regulating vascular tone and oxygen delivery to tissues. The comprehensive analysis of the current understanding of H₂S in atherosclerosis can pave the way for future research and the development of new therapeutic strategies for this debilitating condition. PROSPERO ID: 417150.

Keywords: hydrogen sulfide; tissue oxygenation; hypoxia; atherosclerosis; homeostatic imbalances

1. Introduction

Atherosclerosis is a multifactorial disease involving various cellular and molecular processes, including lipid metabolism, inflammation [1], mitochondrial dysfunction, autophagy, apoptosis, and epigenetics [2]. These processes can induce oxidative stress, which is characterized by an imbalance between oxidants and antioxidants in the body [3], leading to the generation of reactive oxygen species (ROS), reactive nitrogen species (RNS), and other free radicals that can cause damage to cellular components, including proteins, lipids, and DNA [4]. Mitochondrial dysfunction plays a crucial role in atherosclerosis as mitochondria are the primary source of ROS production [5]. These mechanisms contribute to the development and progression of atherosclerosis, characterized by

The interaction between H₂S and nitric oxide is one of the strongest mechanistic arguments for cardiovascular relevance. H₂S can support endothelial function, influence eNOS activity, preserve nitric oxide bioavailability, activate potassium channels, and promote vascular smooth muscle relaxation. In conditions of oxidative stress, endothelial nitric oxide synthase may become uncoupled, reducing NO production and increasing reactive oxygen species. H₂S appears to participate in the preservation of redox balance and may help maintain physiological vasodilatory signaling. This is highly relevant for cardiovascular rehabilitation, peripheral vascular dysfunction, metabolic syndrome, and aging-related endothelial impairment.



Citation: Munteanu, C. Hydrogen Sulfide and Oxygen Homeostasis in Atherosclerosis: A Systematic Review from Molecular Biology to Therapeutic Perspectives. *Int. J. Mol. Sci.* **2023**, *24*, 8376. <https://doi.org/10.3390/ijms24098376>

Academic Editor: Ida Daniela Perrotta

Received: 16 April 2023

Revised: 3 May 2023

Accepted: 5 May 2023

Published: 6 May 2023



Review

Hydrogen Sulfide Modulation of Matrix Metalloproteinases and CD147/EMMPRIN: Mechanistic Pathways and Impact on Atherosclerosis Progression

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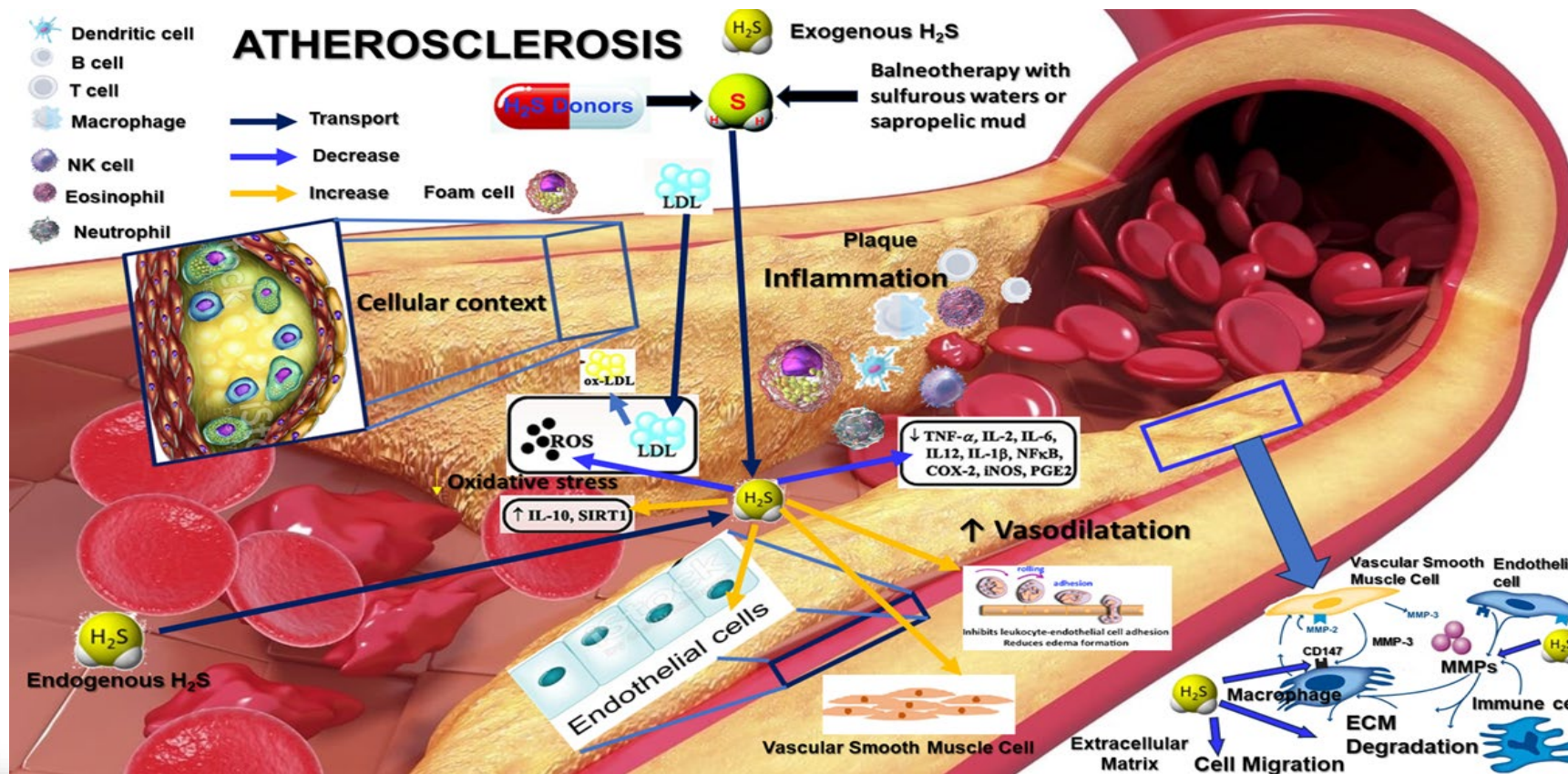
Abstract: Atherosclerosis is a chronic inflammatory condition marked by endothelial dysfunction, lipid accumulation, inflammatory cell infiltration, and extracellular matrix (ECM) remodeling within arterial walls, leading to plaque formation and potential cardiovascular events. Key players in ECM remodeling and inflammation are matrix metalloproteinases (MMPs) and CD147/EMMPRIN, a cell surface glycoprotein expressed on endothelial cells, vascular smooth muscle cells (VSMCs), and immune cells, that regulates MMP activity. Hydrogen sulfide (H₂S), a gaseous signaling molecule, has emerged as a significant modulator of these processes including oxidative stress mitigation, inflammation reduction, and vascular remodeling. This systematic review investigates the mechanistic pathways through which H₂S influences MMPs and CD147/EMMPRIN and assesses its impact on atherosclerosis progression. A comprehensive literature search was conducted across PubMed, Scopus, and Web of Science databases, focusing on studies examining H₂S modulation of MMPs and CD147/EMMPRIN in atherosclerosis contexts. Findings indicate that H₂S modulates MMP expression and activity through transcriptional regulation and post-translational modifications, including S-sulfhydration. By mitigating oxidative stress, H₂S reduces MMP activation, contributing to plaque stability and vascular remodeling. H₂S also downregulates CD147/EMMPRIN expression via transcriptional pathways, diminishing inflammatory responses and vascular cellular proliferation within plaques. The dual regulatory role of H₂S in inhibiting MMP activity and downregulating CD147 suggests its potential as a therapeutic agent in stabilizing atherosclerotic plaques and mitigating inflammation. Further research is warranted to elucidate the precise molecular mechanisms and to explore H₂S-based therapies for clinical application in atherosclerosis.

Keywords: hydrogen sulfide (H₂S); matrix metalloproteinases (MMPs); CD147/EMMPRIN; atherosclerosis; inflammation; vascular remodeling

1. Introduction

Atherosclerosis is a chronic inflammatory disease that primarily affects large and medium-sized arteries. It is characterized by the accumulation of lipids, inflammatory cells, and fibrous elements within the arterial wall, leading to the formation of atherosclerotic plaques [1–5]. The disease progresses through a series of stages, beginning with endothelial dysfunction, then plaque formation, and culminating in vascular remodeling. Understanding these stages is crucial for developing targeted therapies to mitigate the progression and consequences of atherosclerosis [6,7].

Atherosclerosis is not merely lipid deposition. It is an inflammatory, oxidative, endothelial, immune, and metabolic process. H₂S signaling intersects with all these levels. It may influence macrophage activity, leukocyte adhesion, oxidative stress, smooth muscle cell behavior, matrix remodeling, and vasodilation. In balneology, this provides a plausible mechanistic background for the traditional use of sulfurous therapies in vascular, rheumatic, and chronic inflammatory conditions. However, we must be careful: plausible mechanisms are not the same as definitive clinical proof. They are hypotheses that must guide rigorous clinical research.



Review

Novelties on Neuroinflammation in Alzheimer's Disease–Focus on Gut and Oral Microbiota Involvement

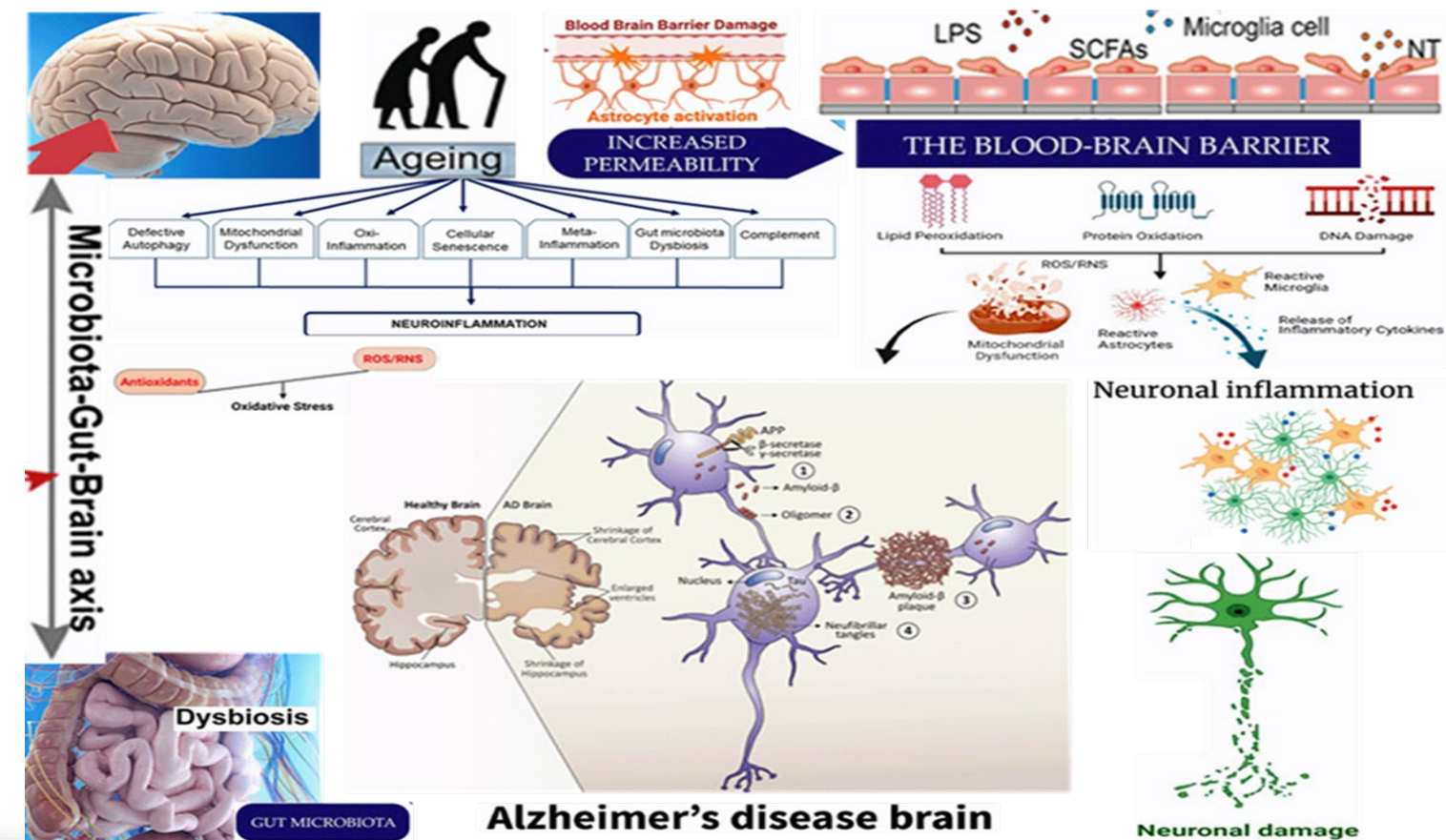
Cristina Popescu ^{1,2,†}, Constantin Munteanu ^{2,3,*}, Aurelian Anghelescu ^{1,2}, Vlad Ciobanu ⁴, Aura Spînu ^{1,2}, Ioana Andone ^{1,2}, Mihaela Mandu ^{1,2,*}, Roxana Bistriceanu ^{1,2}, Mihai Băilă ^{1,2}, Ruxandra-Luciana Postoiu ^{1,2}, Andreea-Iulia Vlădulescu-Trandafir ^{1,2}, Sebastian Giuvara ^{1,2}, Alin-Daniel Malaelea ^{1,2} and Gelu Onose ^{1,2}

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Abstract: Recent studies underscore the role of gut and oral microbiota in influencing neuroinflammation through the microbiota–gut–brain axis, including in Alzheimer's disease (AD). This review aims to provide a comprehensive synthesis of recent findings on the involvement of gut and oral microbiota in the neuroinflammatory processes associated with AD, emphasizing novel insights and therapeutic implications. This review reveals that dysbiosis in AD patients' gut and oral microbiota is linked to heightened peripheral and central inflammatory responses. Specific bacterial taxa, such as Bacteroides and Firmicutes in the gut, as well as Porphyromonas gingivalis in the oral cavity, are notably altered in AD, leading to significant changes in microglial activation and cytokine production. Gut microbiota alterations are associated with increased intestinal permeability, facilitating the translocation of endotoxins like lipopolysaccharides (LPS) into the bloodstream and exacerbating neuroinflammation by activating the brain's toll-like receptor 4 (TLR4) pathways. Furthermore, microbiota-derived metabolites, including short-chain fatty acids (SCFAs) and amyloid peptides, can cross the blood-brain barrier and modulate neuroinflammatory responses. While microbial amyloids may contribute to amyloid-beta aggregation in the brain, certain SCFAs like butyrate exhibit anti-inflammatory properties, suggesting a potential therapeutic avenue to mitigate neuroinflammation. This review not only highlights the critical role of microbiota in AD pathology but also offers a ray of hope by suggesting that modulating gut and oral microbiota could represent a novel therapeutic strategy for reducing neuroinflammation and slowing disease progression.

Keywords: Alzheimer's disease (AD); neuroinflammation; gut microbiota; dysbiosis; amyloid peptides

H₂S is produced by sulfate-reducing bacteria and other microbial pathways. In physiological amounts, microbiota-derived H₂S may participate in mucosal integrity, epithelial function, mucus protection, and „immune regulation. In excessive or dysregulated contexts, however, H₂S may contribute to mucosal injury, inflammation, or dysbiosis. This again illustrates the central principle: biological effects depend on dose, compartment, timing, and context. It also supports the idea that internal crenotherapy with sulfurous waters must be individualized and medically supervised.



Citation: Popescu, C.; Munteanu, C.; Anghelescu, A.; Ciobanu, V.; Spînu, A.; Andone, I.; Mandu, M.; Bistriceanu, R.; Băilă, M.; Postoiu, R.-L.; et al. Novelties on Neuroinflammation in Alzheimer's Disease–Focus on Gut and Oral Microbiota Involvement. *Int. J. Mol. Sci.* **2024**, *25*, 11272. <https://doi.org/10.3390/ijms25011272>

Academic Editor: David Martin-Hernández

Received: 23 September 2024
Revised: 5 October 2024
Accepted: 17 October 2024
Published: 19 October 2024

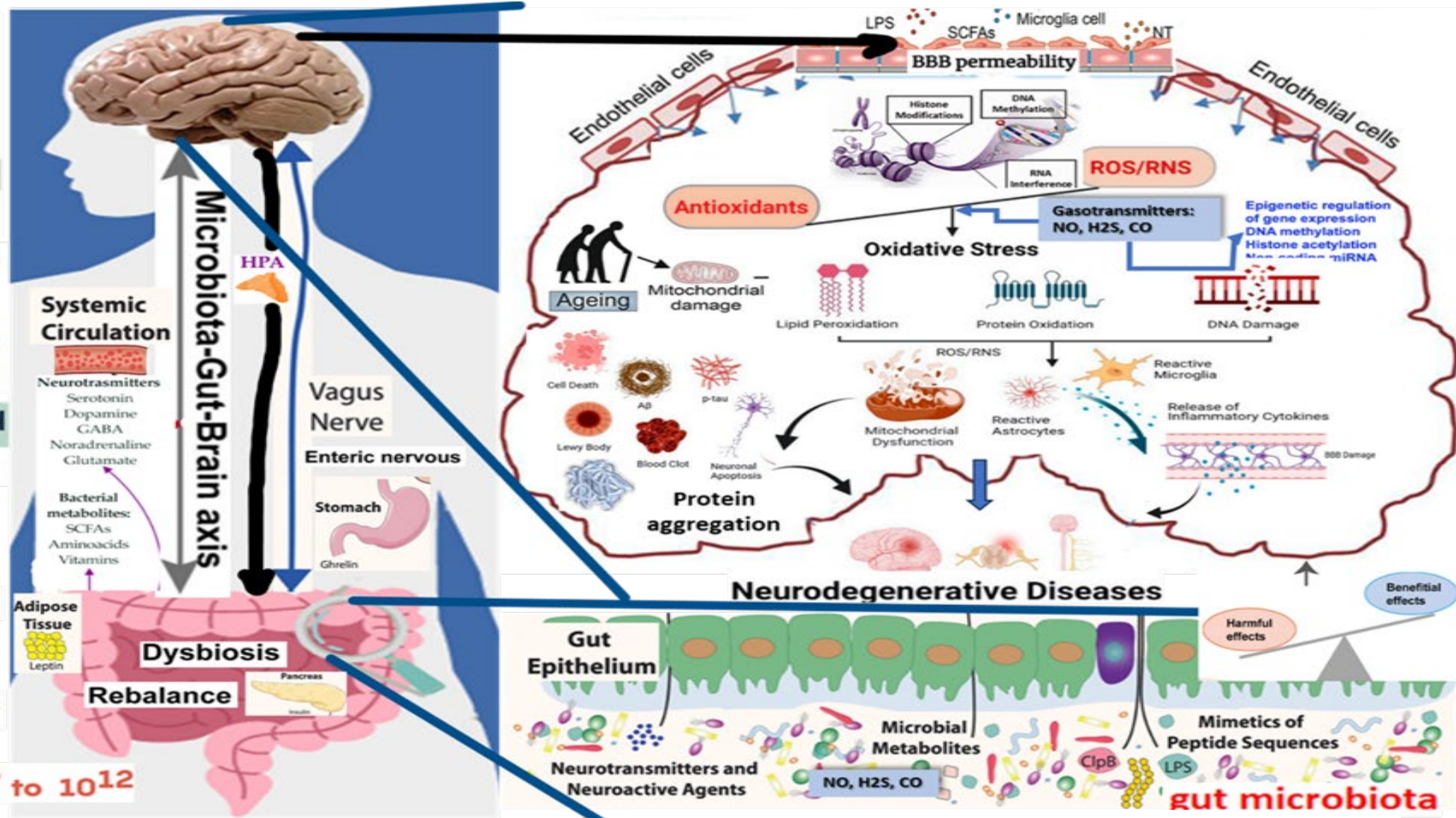
Diet
FMT
Probiotics
Prebiotics
Synbiotics
Postbiotics

Diet, nutrients and other environmental agents such as toxic chemicals, pharmacological factors

Intestinal Microflora

10^{14} microorganisms, >500 species

Lactobacilli	Stomach	10^2 to 10^3
Streptococci	Duodenum	$< 10^4-5$
Lactobacilli	Jejunum	
Enterobacteria	Ileum	10^3 to 10^7
Enterococcus		
Faecalis		
Bacteroides		
Bifidobacteria		
Peptococcus		
Peptostreptococ		
Ruminococcus		
Clostridia		
Lactobacilli	Colon & appendix	10^9 to 10^{12}



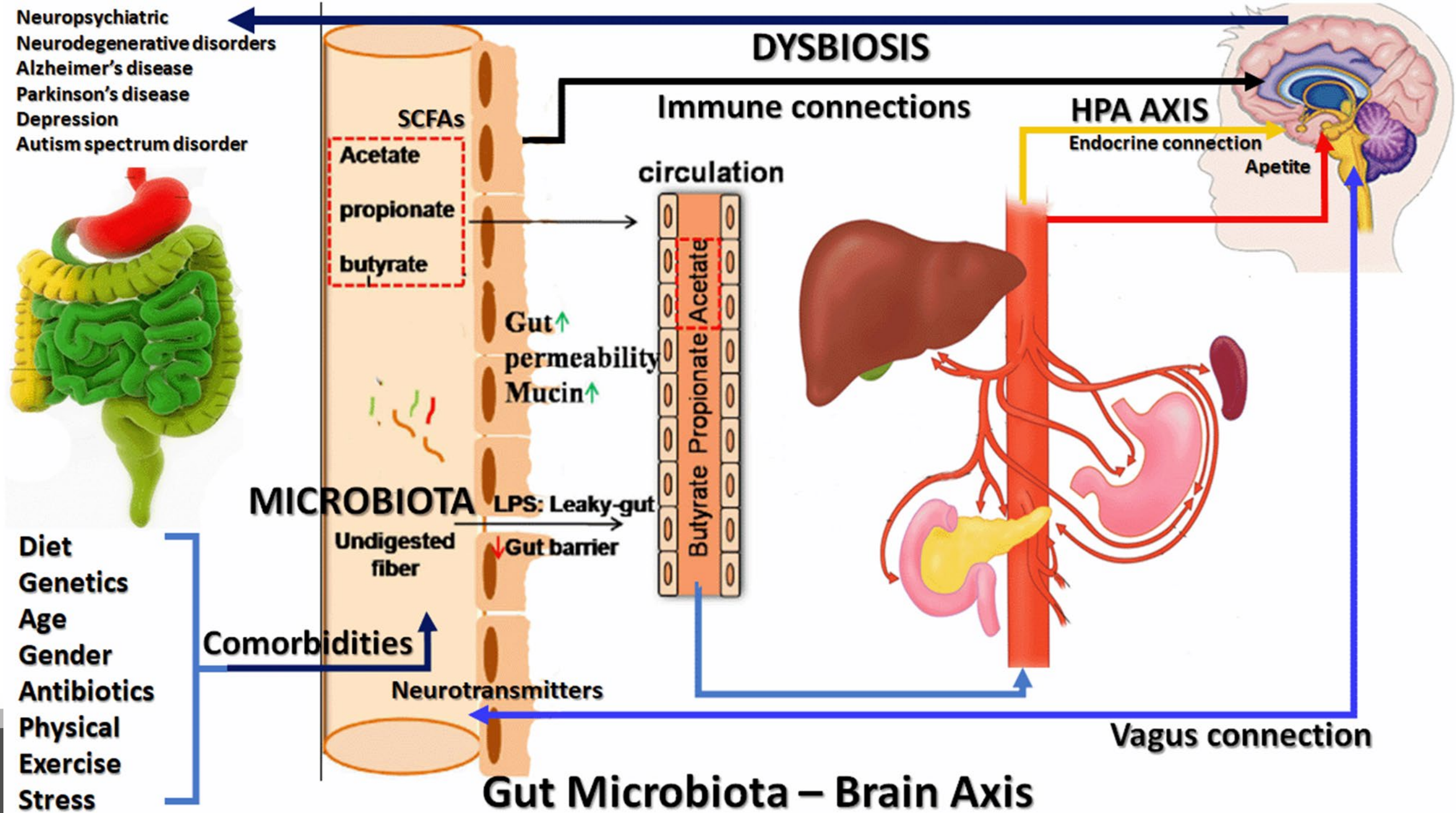
antioxidants

MDPI

Systematic Review

Redox Homeostasis, Gut Microbiota, and Epigenetics in Neurodegenerative Diseases: A Systematic Review

Constantin Munteanu ^{1,2,*}, Anca Irina Galaction ¹, Marius Turnea ¹, Corneliu Dan Blendea ^{3,*}, Mariana Rotariu ¹ and Mădălina Poștaru ¹

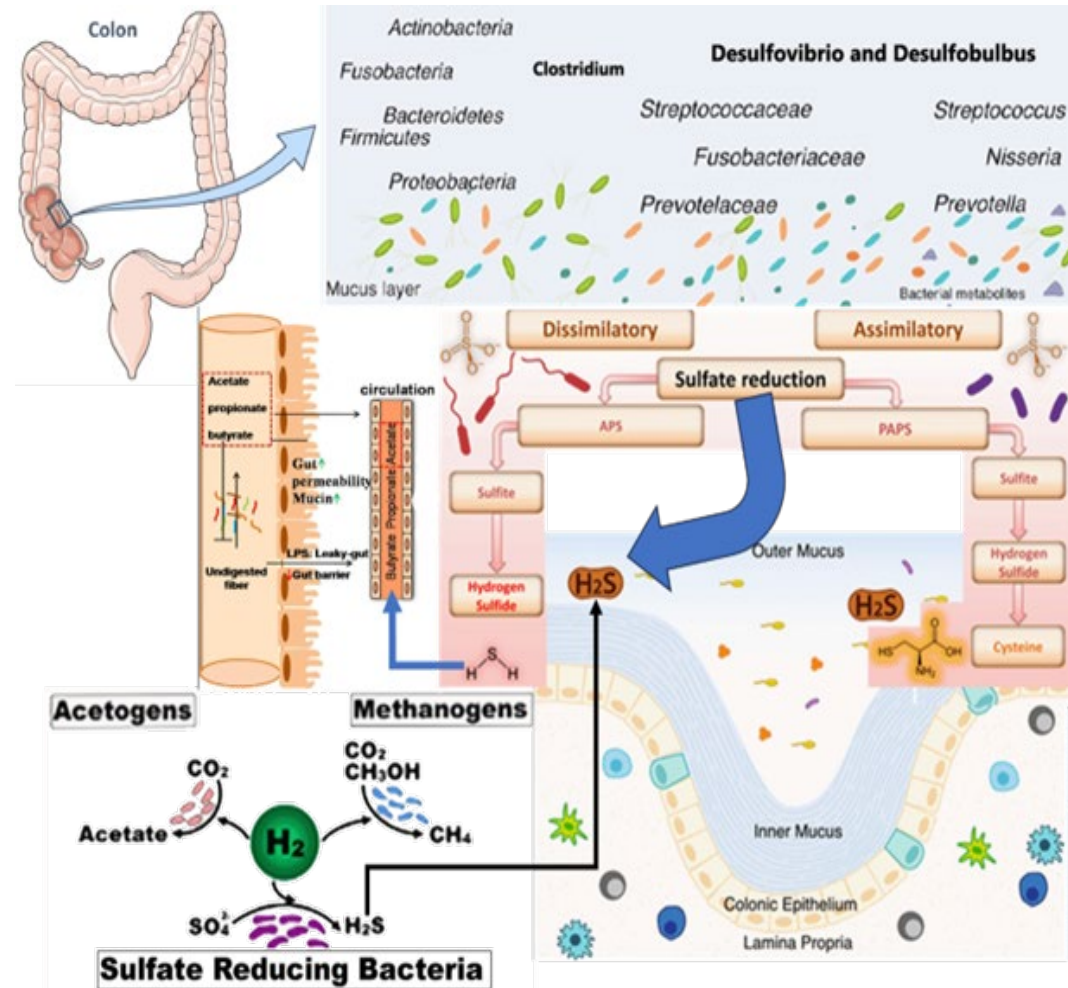




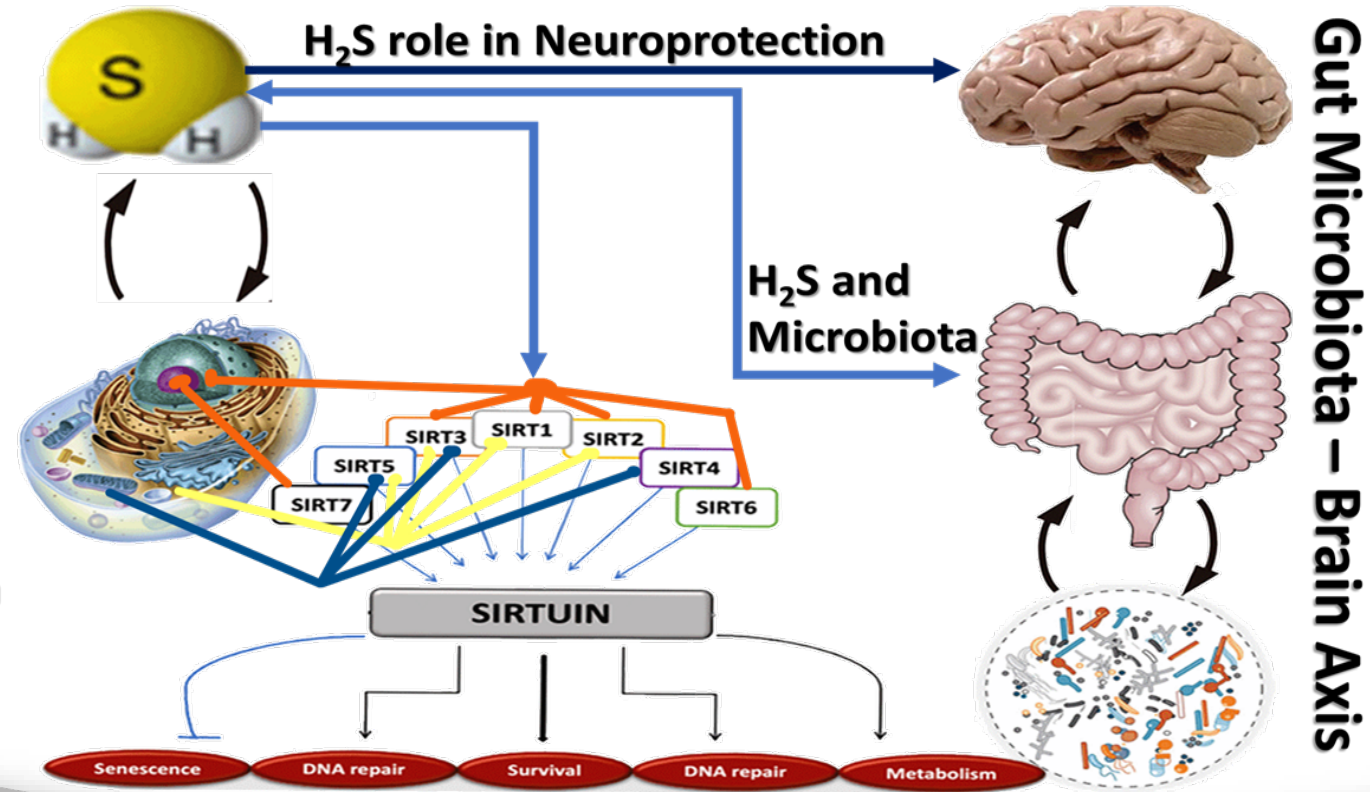
Systematic Review

Hydrogen Sulfide and Gut Microbiota: Their Synergistic Role in Modulating Sirtuin Activity and Potential Therapeutic Implications for Neurodegenerative Diseases

Constantin Munteanu ^{1,2,*}, Gelu Onose ^{2,3}, Mădălina Poștaru ¹, Marius Turnea ¹, Mariana Rotariu ^{1,*} and Anca Irina Galaction ¹



H_2S – Sirtuins Axis



- Regulate mucosal integrity
- Support the anti-inflammatory environment
- Maintain the protective mucus layer
- Regulates epithelial cell proliferation and wound healing
- Support intestinal epithelial barrier function

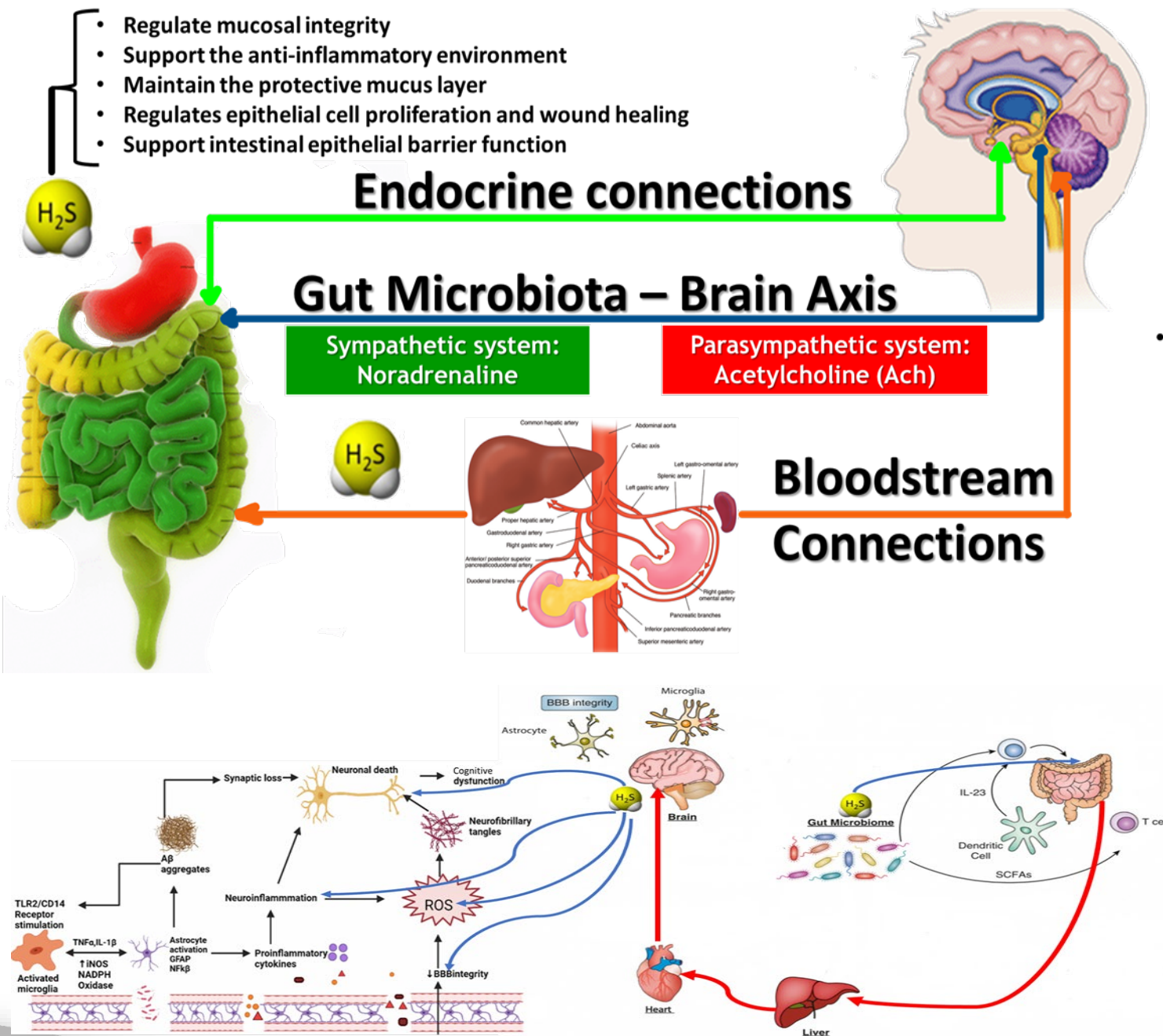
Endocrine connections

Gut Microbiota – Brain Axis

Sympathetic system:
Noradrenaline

Parasympathetic system: Acetylcholine (Ach)

Bloodstream Connections



Review

The Janus Face of Oxidative Stress and Hydrogen Sulfide: Insights into Neurodegenerative Disease Pathogenesis

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Abstract: Oxidative stress plays an essential role in neurodegenerative pathophysiology, acting as both a critical signaling mediator and a driver of neuronal damage. Hydrogen sulfide (H_2S), a versatile gasotransmitter, exhibits a similarly “Janus-faced” nature, acting as a potent antioxidant and cytoprotective molecule at physiological concentrations, but becoming detrimental when dysregulated. This review explores the dual roles of oxidative stress and H_2S in normal cellular physiology and pathophysiology, focusing on neurodegenerative disease progression. We highlight potential therapeutic opportunities for targeting redox and sulfur-based signaling systems in neurodegenerative diseases by elucidating the intricate balance between these opposing forces.

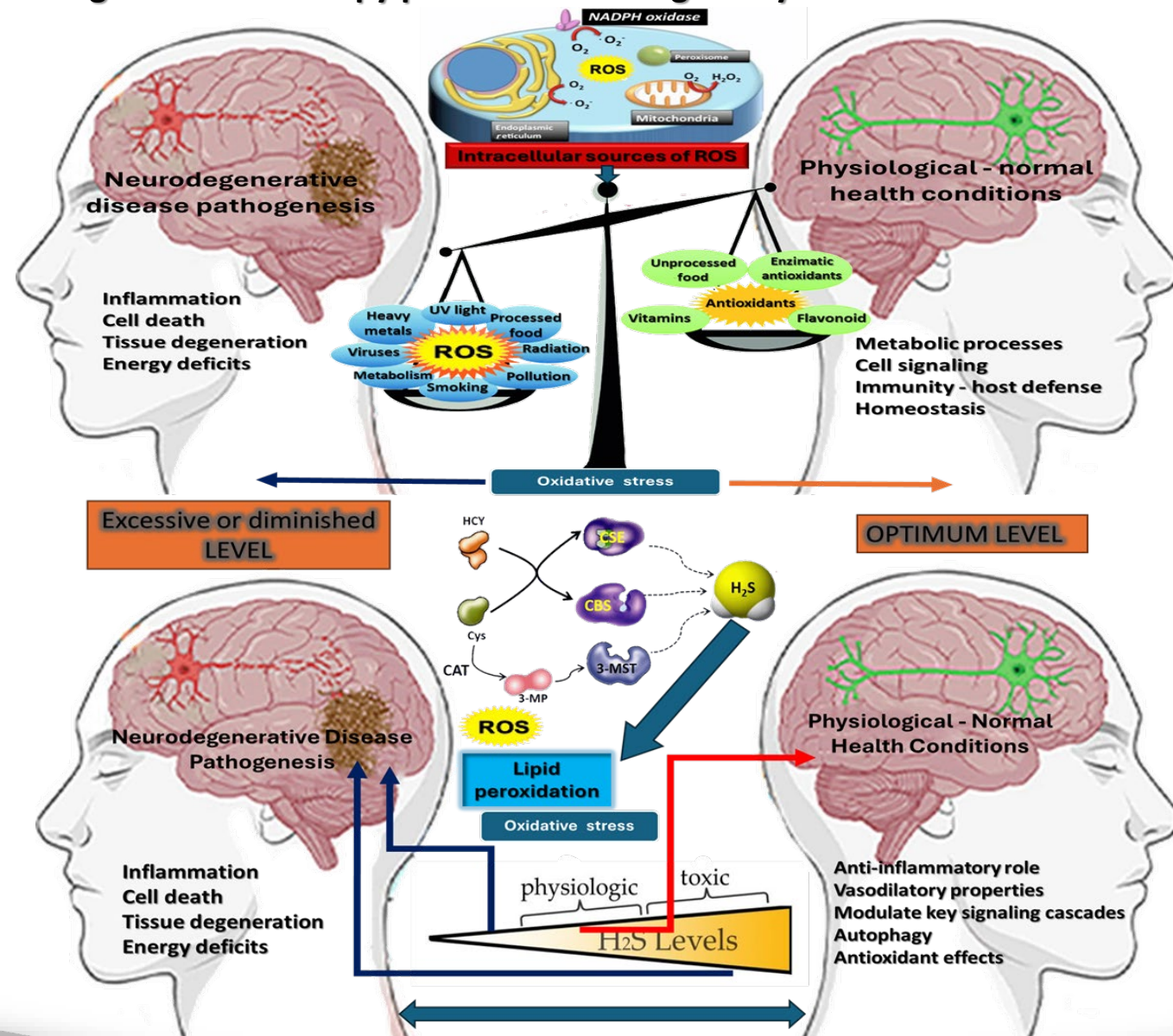
Keywords: oxidative stress; hydrogen sulfide (H_2S); neurodegenerative diseases; redox signaling; Janus face; neuroinflammation

1. Introduction

Neurodegenerative disorders, such as Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis (ALS), are a growing medical challenge worldwide [1–3]. These conditions are typically characterized by progressive neuronal loss, accumulation of misfolded or aggregated proteins, peroxisomal dysfunction [4,5], and persistent neuroinflammation [6–10]. While each disorder has distinct clinical features—ranging from cognitive decline to motor dysfunction, there is an overarching theme that oxidative stress contributes significantly to the pathological cascades involved [11–13]. Excessive ROS in the central nervous system (CNS) can damage neuronal membranes through lipid peroxidation, alter synaptic function, and potentially accelerate protein misfolding [14–17].

Concurrently, the inflammatory microenvironment within the brain can exacerbate

Some clinical balneological literature distinguishes low-concentration sulfurous waters used internally from higher-concentration waters used externally, while also noting that crenotherapy protocols are not globally standardized.



Academic Editor: Marco Fiore

Received: 27 February 2025

Revised: 9 March 2025

Accepted: 17 March 2025

Published: 19 March 2025

Citation: Munteanu, C.; Galaction, A.I.; Onose, G.; Turnea, M.; Rotariu, M. The Janus Face of Oxidative Stress and Hydrogen Sulfide: Insights into Neurodegenerative Disease Pathogenesis. *Antioxidants* **2025**, *14*, 360. <https://doi.org/10.3390/>

Harnessing Gasotransmitters to Combat Age-Related Oxidative Stress in Smooth Muscle and Endothelial Cells

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Abstract: Age-related oxidative stress is a critical factor in vascular dysfunction, contributing to hypertension and atherosclerosis. Smooth muscle cells and endothelial cells are particularly susceptible to oxidative damage, which exacerbates vascular aging through cellular senescence, chronic inflammation, and arterial stiffness. Gasotransmitters—hydrogen sulfide (H₂S), nitric oxide (NO), and carbon monoxide (CO)—are emerging as promising therapeutic agents for counteracting these processes. This review synthesizes findings from recent studies focusing on the mechanisms by which H₂S, NO, and CO influence vascular smooth muscle and endothelial cell function. Therapeutic strategies involving exogenous gasotransmitter delivery systems and combination therapies were analyzed. H₂S enhances mitochondrial bioenergetics, scavenges ROS, and activates antioxidant pathways. NO improves endothelial function, promotes vasodilation, and inhibits platelet aggregation. CO exhibits cytoprotective and anti-inflammatory effects by modulating heme oxygenase activity and ROS production. In preclinical studies, gasotransmitter-releasing molecules (e.g., NaHS, SNAP, CORMs) and targeted delivery systems show significant promise. Synergistic effects with lifestyle modifications and antioxidant therapies further enhance their therapeutic potential. In conclusion, gasotransmitters hold significant promise as therapeutic agents to combat age-related oxidative stress in vascular cells. Their multifaceted mechanisms and innovative delivery approaches make them potential candidates for treating vascular dysfunction and promoting healthy vascular aging. Further research is needed to translate these findings into clinical applications.

Keywords: gasotransmitters; oxidative stress; vascular aging; endothelial cells; smooth muscle cells; hydrogen sulfide; nitric oxide; carbon monoxide



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Academic Editor: Charles E. Norton

Received: 25 January 2025

Revised: 24 February 2025

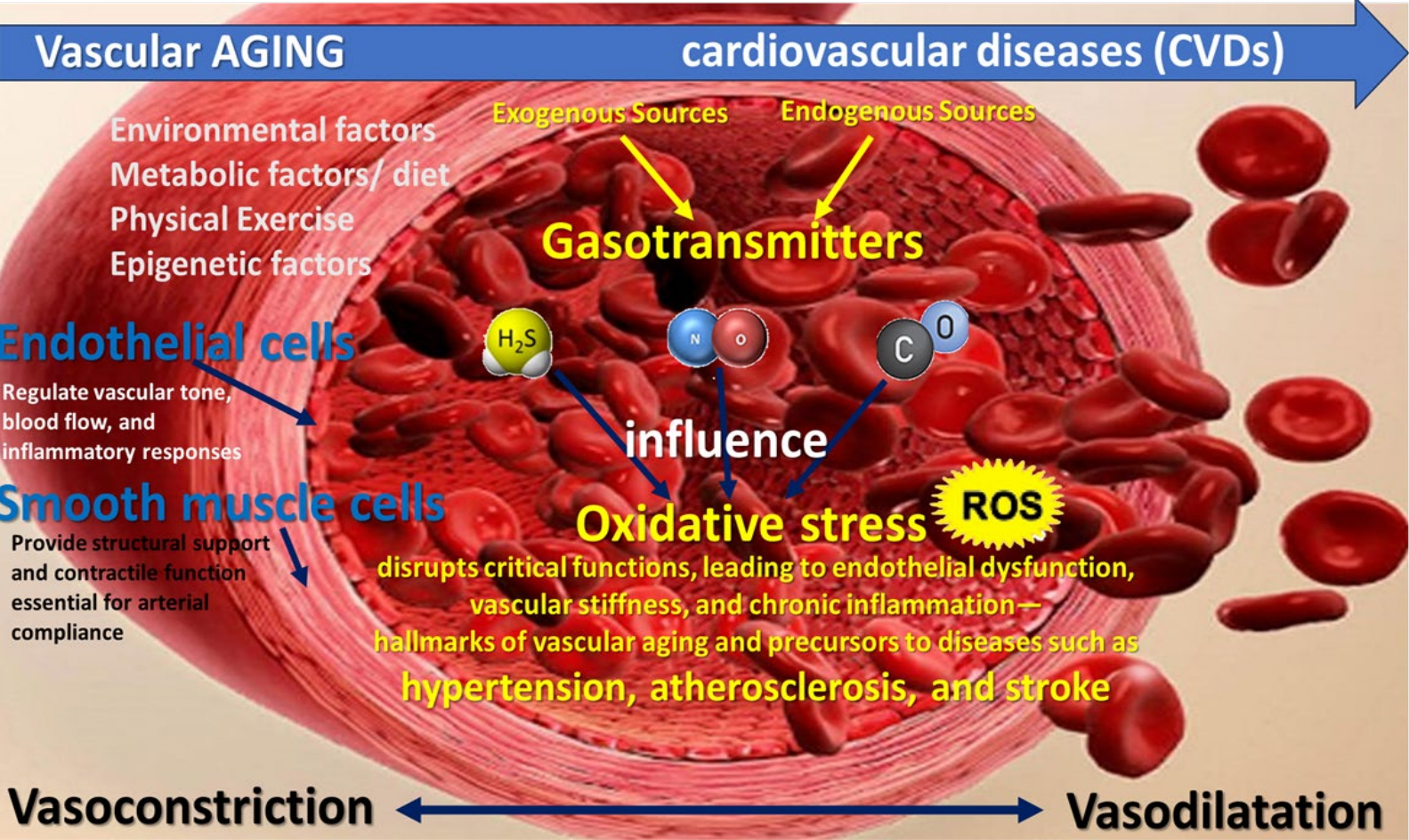
Accepted: 26 February 2025

Published: 27 February 2025

Citation: Munteanu, C.; Galaction, A.I.; Onose, G.; Turnea, M.; Rotariu, M. Harnessing Gasotransmitters to Combat Age-Related Oxidative Stress in Smooth Muscle and Endothelial Cells. *Pharmaceuticals* **2025**, *18*, 344.

1. Introduction

This brings us to safety. H₂S is biologically active because it is chemically reactive. The same property that gives it signaling capacity also explains its toxicity at high concentrations. Therefore, the clinical use of sulfurous waters requires precise knowledge of concentration, route of administration, ventilation, exposure duration, contraindications, and patient vulnerability. Balneary H₂S resources should be treated with the same seriousness as any active therapeutic factor. Their natural origin does not eliminate the need for rigorous medical control. On the contrary, it increases the need for standardization because natural resources are variable.



Hydrogen Sulfide (H₂S- or H₂S_n-Polysulfides) in Synaptic Plasticity: Modulation of NMDA Receptors and Neurotransmitter Release in Learning and Memory

Constantin Munteanu ^{1,2,*}, Anca Irina Galaction ¹, Gelu Onose ^{2,3}, Marius Turnea ^{1,*} and Mariana Rotariu ¹

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Abstract: Hydrogen sulfide (H₂S) has emerged as a pivotal gaseous transmitter in the central nervous system, influencing synaptic plasticity, learning, and memory by modulating various molecular pathways. This review examines recent evidence regarding how H₂S regulates NMDA receptor function and neurotransmitter release in neuronal circuits. By synthesizing findings from animal and cellular models, we investigate the impacts of enzymatic H₂S production and exogenous H₂S on excitatory synaptic currents, long-term potentiation, and intracellular calcium signaling. Data suggest that H₂S interacts directly with NMDA receptor subunits, altering receptor function and modulating neuronal excitability. Simultaneously, H₂S promotes the release of neurotransmitters such as glutamate and GABA, shaping synaptic dynamics and plasticity. Furthermore, reports indicate that disruptions in H₂S metabolism contribute to cognitive impairments and neurodegenerative disorders, underscoring the potential therapeutic value of targeting H₂S-mediated pathways. Although the precise mechanisms of H₂S-induced changes in synaptic strength remain elusive, a growing body of evidence positions H₂S as a significant regulator of memory formation processes. This review calls for more rigorous exploration into the molecular underpinnings of H₂S in synaptic plasticity, paving the way for novel pharmacological interventions in cognitive dysfunction.

Keywords: hydrogen sulfide; NMDA receptor; synaptic plasticity; neurotransmitter release; cognitive function



Academic Editors: Volkmar Lessmann and Manuela Dicarlo

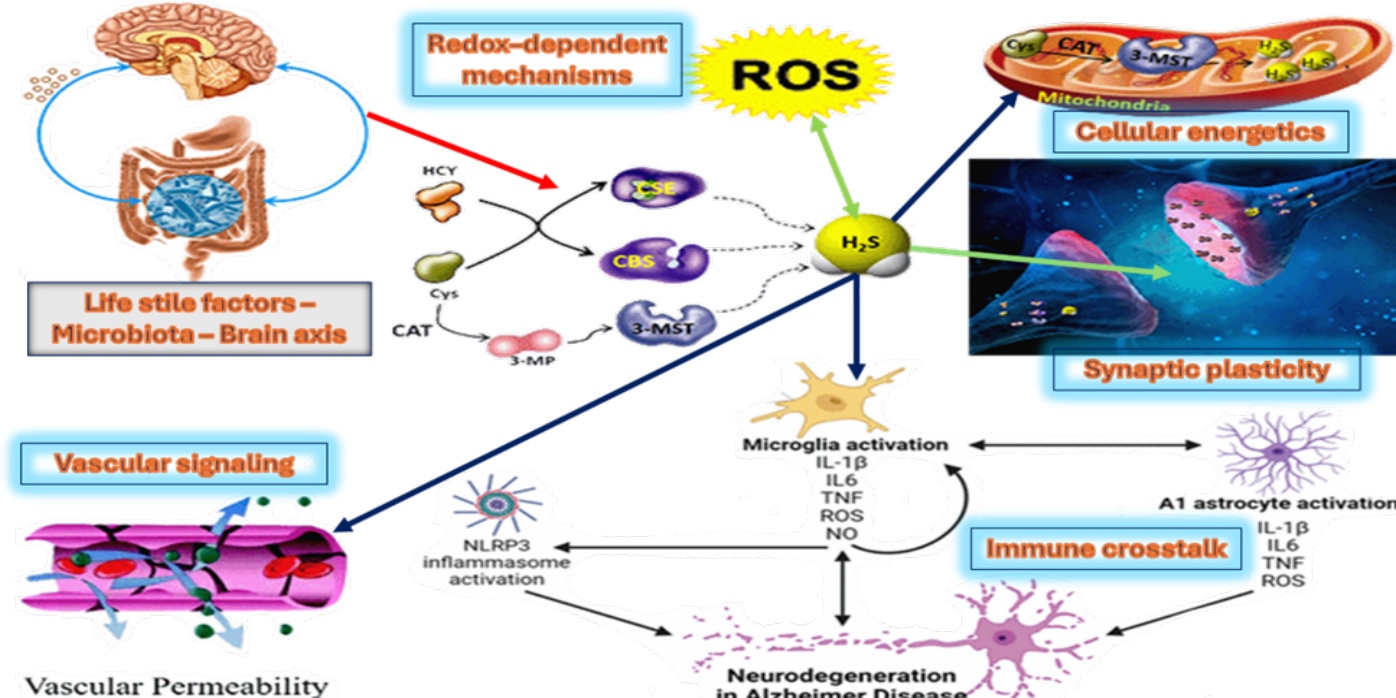
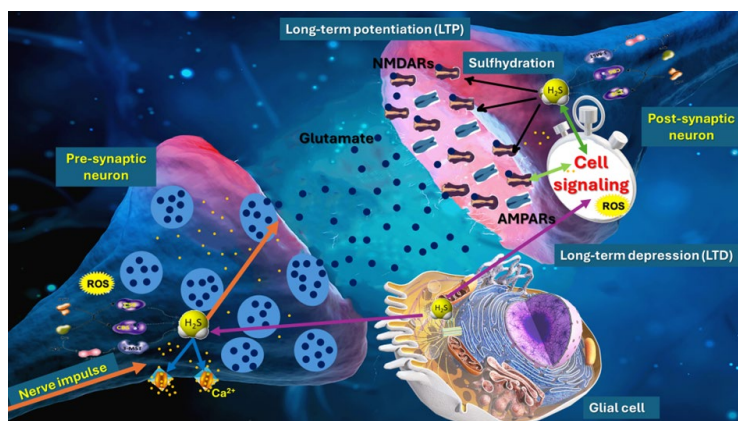
Received: 9 February 2025

Revised: 21 March 2025

Accepted: 26 March 2025

Published: 28 March 2025

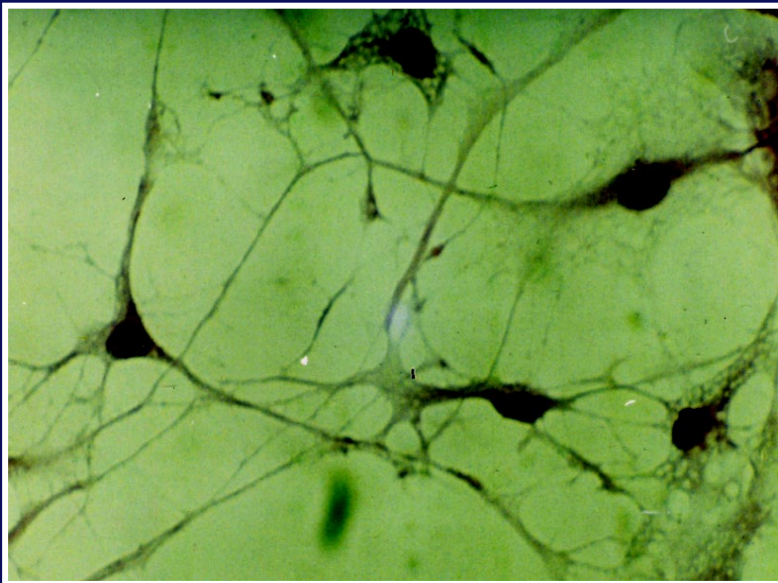
Citation: Munteanu, C.; Galaction, A.I.; Onose, G.; Turnea, M.; Rotariu, M. Hydrogen Sulfide (H₂S- or H₂S_n-Polysulfides) in Synaptic Plasticity: Modulation of NMDA



Hydrogen sulfide is a small molecule with a large biomedical meaning. In the organism, it acts as a gasotransmitter involved in vascular tone, redox homeostasis, mitochondrial regulation, inflammation, metabolism, and neurobiology. In balneology, it appears as an exogenous natural therapeutic factor in sulfurous waters and therapeutic muds. Romania has diverse sulfurous resources that deserve renewed scientific attention, not only as elements of tradition, but as resources for modern, mechanism-based, evidence-oriented rehabilitation medicine.

We must preserve the natural therapeutic factors, characterize them precisely, study them rigorously, and integrate them responsibly into contemporary medicine. In this way, Romanian balneology can contribute not only to health tourism, but also to preventive medicine, chronic disease management, rehabilitation, and translational biomedical research.

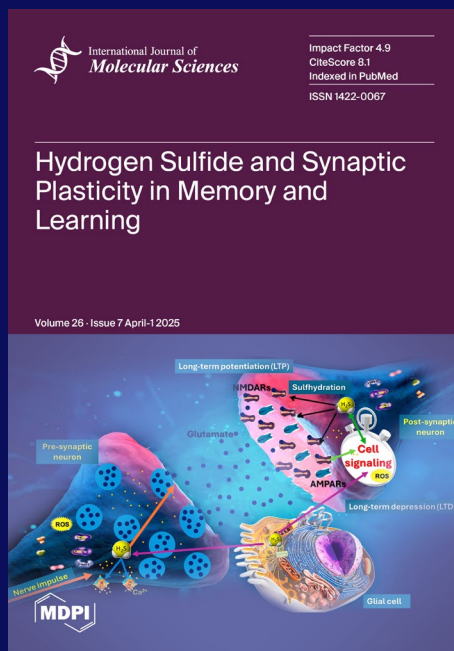
“If we have no passion, we have nothing to start with in life” (*Lin Yutang*)



THANK YOU!



Va mulțumesc mult pentru atenție!



• Conf. univ. dr. biol. Constantin Munteanu