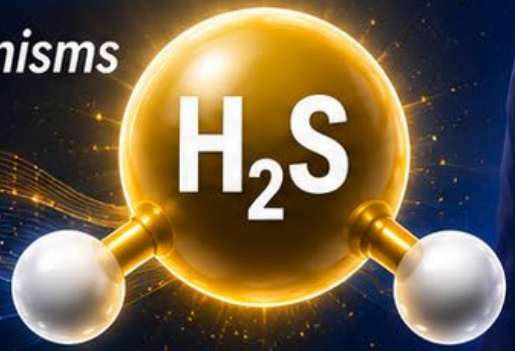
HYDROGEN SULFIDE (H_2S) AND NEURODEGENERATIVE DISEASES

From Molecular Mechanisms to Neuroprotection



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NEUROLOGY AND NEUROLOGICAL DISORDERS

H2S IN BALNEOLOGY GLOBAL INITIATIVE

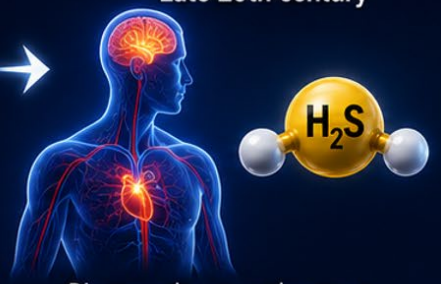
FROM TOXIC GAS TO NEUROPROTECTIVE MOLECULE

The remarkable evolution of hydrogen sulfide (H_2S)

1 TOXIC GAS
19th century

Known as a poisonous gas with a characteristic odor and high toxicity.

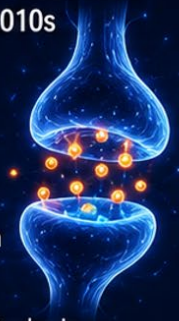
2 ENDOGENOUS MOLECULE
Late 20th century



Discovered as an endogenous gasotransmitter in the human body, similar to NO and CO.

3 SIGNALING MOLECULE
2000s – 2010s

- Vasoregulation
- Anti-inflammation
- Cytoprotection
- Redox homeostasis
- Mitochondrial function
- Neurotransmission



Multiple physiological roles in vascular, metabolic, mitochondrial, and neural regulation.

4 THERAPEUTIC TARGET
2010s – present

- Neuroprotection
- Disease modulation
- Drug development
- Precision medicine

Emerging focus for therapeutic strategies in neurodegenerative diseases and beyond.

PAST
Toxic and dangerous

DISCOVERY
A hidden endogenous messenger

UNDERSTANDING
Complex signaling and physiological roles

FUTURE
Therapeutic potential and clinical translation

From a hazardous gas to a vital signal — H_2S *is a key player in health and disease.*

BALNEO RESEARCH Balneo and PRM Research Journal

Hydrogen sulfide (H_2S) - 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 H_2S, a hormetic gaseous molecule that can actively penetrate the skin. While high levels of H_2S 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: Cochrane[1], Elsevier[1], NCBI/PubMed[1], NCBI/PMC[4], PEDro[1], and ISI Web of Knowledge/Science[1], 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. H_2S 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 gase. The link between balneotherapy and medical rehabilitation regarding the usage of hydrogen sulfide emphasises the unity for this medical speciality.

Keywords: *Hydrogen sulfide / H_2S AND balneotherapy / inhalations / mud / Rheumatoid arthritis / neuroprotection / neurodegenerative disorders / Stroke / Parkinson / Alzheimer / Huntington / vascular dementia / Immune system / Diabetes / Cancer / Cardioprotection / Asthma / Alergic Rhinitis / COPD / COVID-19 / Burns / Analgesic effect / Clinical trials*

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Biol. Diana Munteanu, Priority research areas: microbiology, balneoclimatology, including the study of natural mineral waters and mofettes, therapeutic muds, and other balneary resources.

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	H_2S		NO		H_2O_2		CO	
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	
	Animals	Plants	Animals	Plants	Animals	Plants	Animals	Plants
Enzymatic production	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 desulfhydrase; 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.

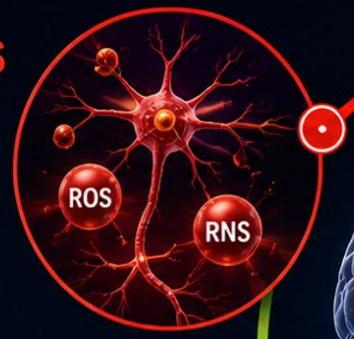
- **Hydrogen sulfide (H_2S) - primarily a toxic gas, recognizable by its characteristic odor – (environmental / occupational hazard).**
- **H_2S - endogenous signaling molecule, comparable to nitric oxide and carbon monoxide.**
- **H_2S - gasotransmitter involved in vascular regulation, redox homeostasis, mitochondrial function, inflammation, cytoprotection, neuromodulation, and cellular adaptation.**

WHY NEURODEGENERATION?

Common Mechanisms Underlying Neurodegenerative Diseases

1 OXIDATIVE STRESS

Excess reactive oxygen and nitrogen species damage proteins, lipids, and DNA.



2 MITOCHONDRIAL DYSFUNCTION

Impaired energy production, increased ROS, and defective mitophagy lead to neuronal injury.

3 NEUROINFLAMMATION

Activated microglia and chronic inflammation release cytokines that promote neuronal damage and synaptic loss.

4 PROTEIN AGGREGATION

Misfolded proteins such as Aβ, tau, α-synuclein, and TDP-43 aggregate, disrupting cellular function and connectivity.

These interconnected mechanisms converge to cause neuronal dysfunction and progressive cognitive decline.

antioxidants

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Review

Signaling Paradigms of H_2S-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 (H_2S), 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 H_2S-induced vasodilation. The vasodilatory effects of H_2S 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, H_2S inhibits L-type calcium channels, reducing calcium influx and diminishing VSMC contraction. Beyond ion channel modulation, H_2S 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 H_2S and nitric oxide (NO) signaling further amplifies vasodilation. H_2S enhances NO bioavailability by inhibiting its degradation and stimulating endothelial nitric oxide synthase (eNOS) activity, increasing cGMP levels and potent vasodilatory responses. Protein sulfhydration, a post-translational modification, plays a crucial role in cell signaling. H_2S S-sulfurates oxidized cysteine residues, while polysulfides (H_2Sn) are responsible for S-sulfurating reduced cysteine residues. Sulfhydration of key proteins like K_{ATP} channels and sGC enhances their activity, contributing to the overall vasodilatory effect. Furthermore, H_2S interaction with endothelium-derived hyperpolarizing factor (EDHF) pathways adds another layer to its vasodilatory mechanism. By enhancing EDHF activity, H_2S facilitates the hyperpolarization and relaxation of VSMCs through gap junctions between endothelial cells and VSMCs. Recent findings suggest that H_2S can also modulate transient receptor potential (TRP) channels, particularly TRPV4 channels, in endothelial cells. Activating these channels by H_2S promotes calcium entry, stimulating the production of vasodilatory agents like NO and prostacyclin, thereby regulating vascular tone. The comprehensive understanding of H_2S-induced vasodilation mechanisms highlights its therapeutic potential. The multifaceted approach of H_2S in modulating vascular tone presents a promising strategy for developing novel treatments for hypertension, ischemic conditions, and other vascular disorders. The interaction of H_2S with ion channels, cyclic nucleotide signaling, NO pathways, ROS (Reactive Oxygen Species) scavenging, protein sulfhydration, and EDHF underscores its complexity and therapeutic relevance. In conclusion, the intricate signaling paradigms of H_2S-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 (H_2S); vasodilation; protein sulfhydration; ROS scavenging; endothelial function

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Citation: Munteanu, C.; Popescu, C.; Vlădulescu-Trandafir, A.-I.; Onose, G. Signaling Paradigms of H_2S-Induced Vasodilation: A Comprehensive Review. *Antioxidants* **2024**, *13*, 1158. https://doi.org/10.3390/antiox13101158

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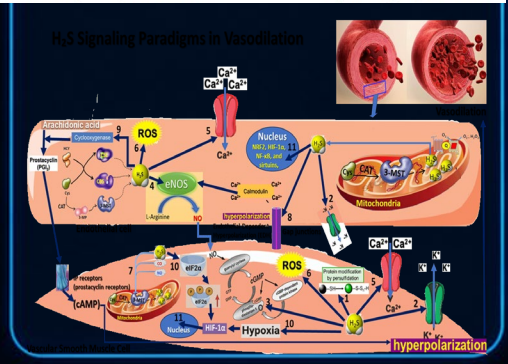


Neurodegenerative diseases share several common mechanisms. Oxidative stress, mitochondrial dysfunction, chronic neuroinflammation, and protein aggregation progressively damage neurons and synaptic networks. H_2S intersects with all of these pathways. This is why it has attracted increasing attention as a systems-level regulator rather than as a single-target therapeutic molecule.

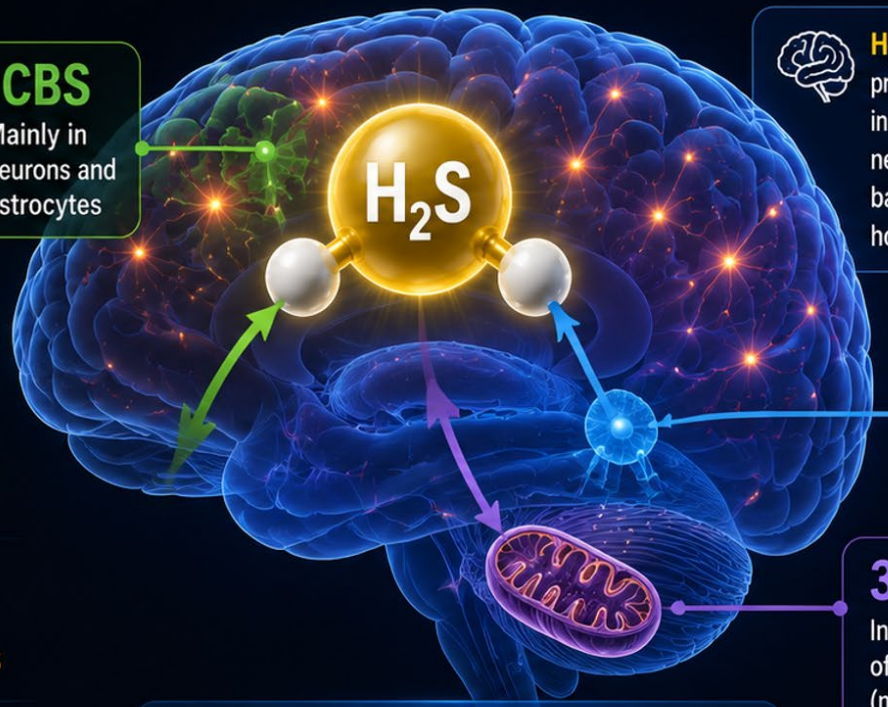
ENDOGENOUS H_2S IN THE BRAIN

H_2S is synthesized in the brain by three major enzymes

1. **CBS – Cystathionine β-Synthase**
   Location: Neurons, astrocytes, vascular cells
   Reaction: L-homocysteine + L-serine → cystathionine → cysteine → H_2S

2. **CSE – Cystathionine γ-Lyase**
   Location: Neurons, astrocytes, microglia
   Reaction: L-cysteine → pyruvate + NH_3 + H_2S

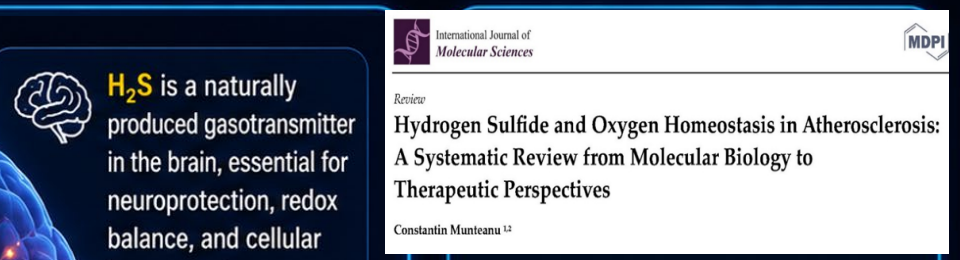
3. **3-MST – 3-Mercaptopyruvate Sulfurtransferase**
   Location: Mitochondria (highly expressed)
   Reaction: 3-mercaptopyruvate + sulfane sulfur → pyruvate + H_2S



Physiological Roles of Brain-Derived H_2S

Neuroprotection | Vasoregulation | Neurotransmission | Mitochondrial function | Anti-inflammation

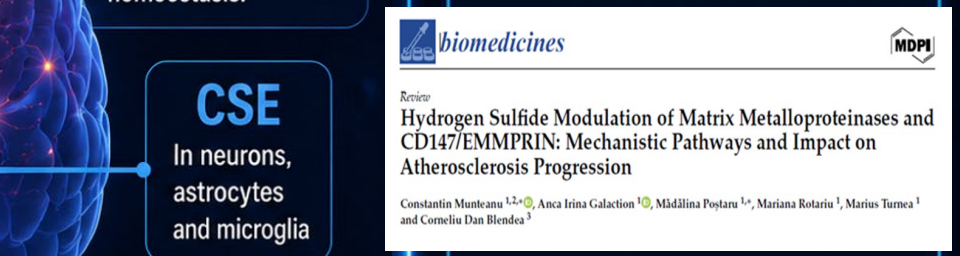
Endogenous H_2S production is essential for optimal brain function and protection against neurodegenerative processes.


International Journal of Molecular Sciences — MDPI

Review

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

Constantin Munteanu [1,2]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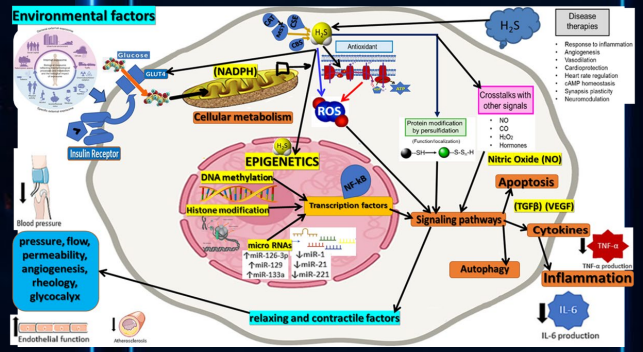
Review

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

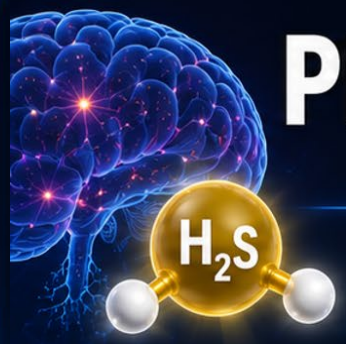
Constantin Munteanu [1,2,*], Anca Irina Galaction [1], Mădălina Poștaru [1,*], Mariana Rotariu [1], Marius Turnea [1] and Corneliu Dan Blendea [3]



H_2S is naturally produced in the central nervous system through the enzymes CBS, CSE, and 3-MST. These enzymatic systems are distributed among neurons, astrocytes, microglia, and mitochondria. Endogenous H_2S contributes to neurotransmission, neurovascular regulation, mitochondrial function, and antioxidant defense. Therefore, H_2S should be viewed as an integral component of normal brain physiology.

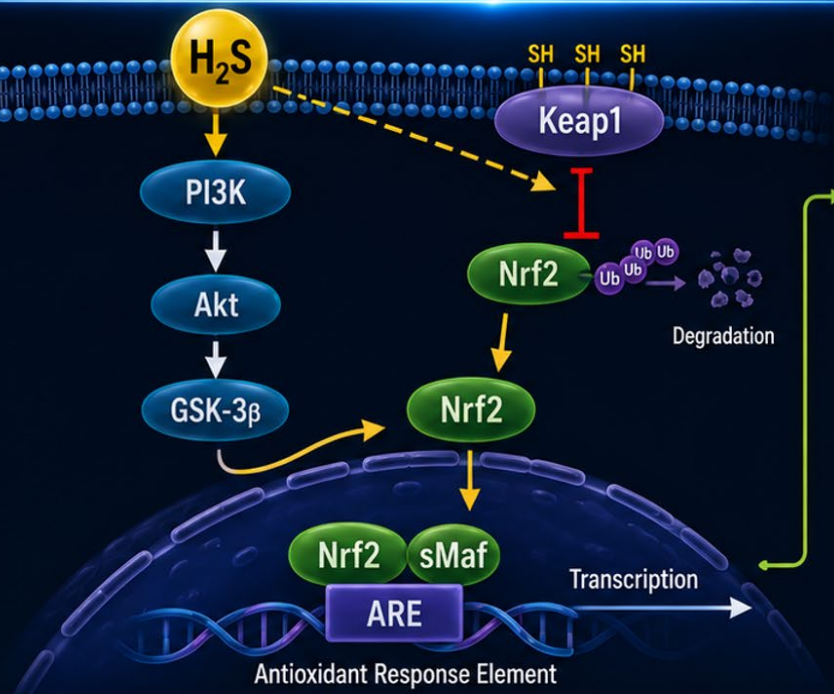
PILLAR 1: REDOX HOMEOSTASIS

H_2S Activates Nrf2 and Strengthens Antioxidant Defenses



H_2S TRIGGERS Nrf2 ACTIVATION

- Enhances antioxidant enzyme expression
- Reduces oxidative stress
- Maintains redox balance
- Prevents neuronal damage
- Promotes neuronal survival and function



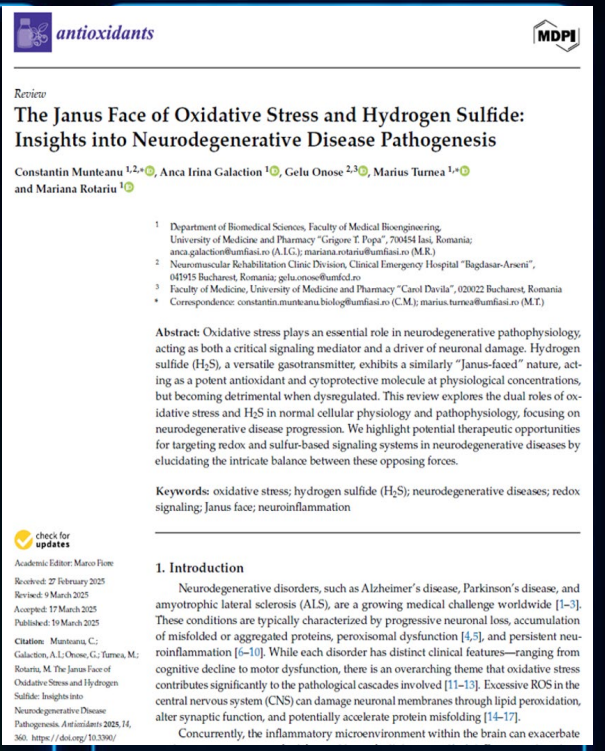
UPREGULATION OF ANTIOXIDANT GENES

- **HO-1** Heme Oxygenase-1
- **NQO1** NAD(P)H Quinone Oxidoreductase 1
- **SOD** Superoxide Dismutase
- **CAT** Catalase
- **GPx** Glutathione Peroxidase

OUTCOMES

- Enhanced Antioxidant Defense
- Restored Redox Balance
- Reduced Oxidative Damage
- Neuronal Protection and Survival
- Improved Neuronal Function

H_2S–Nrf2 SIGNALING IS A CENTRAL PATHWAY FOR REDOX HOMEOSTASIS AND A FOUNDATION OF NEUROPROTECTION.



antioxidants MDPI

Review

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

Constantin Munteanu [1,2,*], Anca Irina Galaction [1], Gelu Onose [2,3], Marius Turnea [1,*] and Mariana Rotariu [1]

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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

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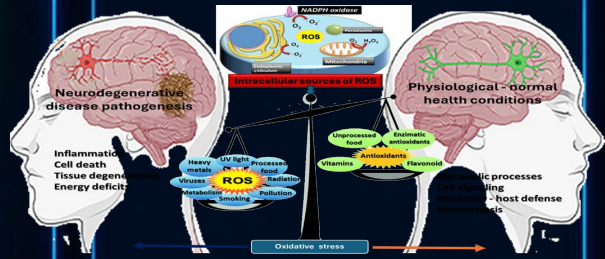
1. Introduction

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].

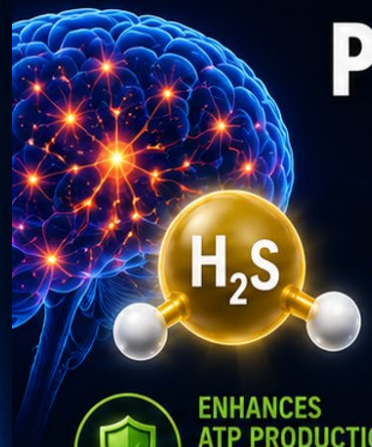
Concurrently, the inflammatory microenvironment within the brain can exacerbate



One of the most important functions of H_2S is the regulation of redox homeostasis. H_2S activates Nrf2-dependent signaling and promotes the expression of antioxidant enzymes such as HO-1, NQO1, SOD, catalase, and glutathione-related pathways. Through these mechanisms, H_2S may help limit oxidative damage and preserve neuronal survival under stressful conditions.

PILLAR 2: MITOCHONDRIAL DYSFUNCTION

H_2S Supports Mitochondrial Health and Energy Production



HOW H_2S SUPPORTS MITOCHONDRIA

ENHANCES ATP PRODUCTION
Optimizes electron transport chain efficiency.

MAINTAINS MEMBRANE POTENTIAL
Preserves mitochondrial integrity and function.

REDUCES OXIDATIVE STRESS
Directly scavenges ROS and boosts antioxidant defenses.

REGULATES MITOCHONDRIAL DYNAMICS
Promotes balanced fission and fusion for quality control.

PROMOTES MITOPHAGY
Facilitates removal of damaged mitochondria and cellular renewal.

IMPROVES ENERGY METABOLISM
Supports efficient glucose and fatty acid utilization.

OUTCOMES

- Increased Energy Production
- Enhanced Cellular Resilience
- Protection Against Mitochondrial-Mediated Damage
- Improved Neuronal Function and Survival
- Support for Neurodegenerative Disease Prevention

H_2S By preserving mitochondrial function, H_2S ensures the energy and resilience neurons need to survive and thrive.

current issues in molecular biology — MDPI

Review

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

Constantin Munteanu [1,2,*], Mariana Rotariu [1], Marius-Alexandru Turnea [1], Aurelian Anghelescu [2,3], Irina Albadi [4,5], Gabriela Dogaru [6,7], Sînziana Calina Silișteanu [8], Elena Valentina Ionescu [3,9], Florentina Carmen Firan [10], Anca Mirela Ionescu [11], Carmen Oprea [4,9] and Gelu Onose [2,11,*]

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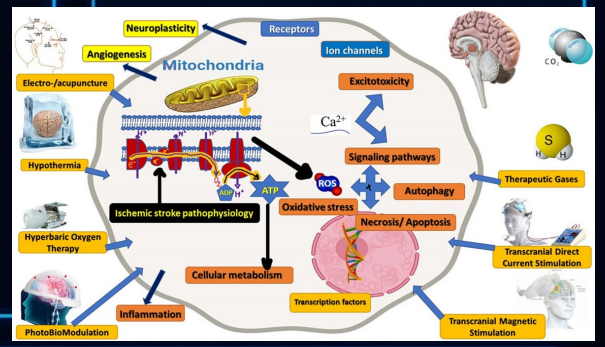
Abstract: Diabetes mellitus (DM) is a frequent medical problem, affecting more than 4% of the population in most countries. In the context of diabetes, the vascular endothelium can play a crucial pathophysiological role. If a healthy endothelium—which is a dynamic endocrine organ with autocrine and paracrine 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



Mitochondria are central targets of H_2S signaling. Physiological concentrations of H_2S may support electron transport, ATP production, mitophagy, and mitochondrial quality control. Since mitochondrial dysfunction is a hallmark of neurodegeneration, preserving mitochondrial resilience is one of the most attractive therapeutic aspects of H_2S biology.

PILLAR 3: NEUROINFLAMMATION CONTROL

NEURO CONCLAVE 2026
NEUROLOGY AND NEUROLOGICAL DISORDERS

H_2S MODULATES MICROGLIAL ACTIVATION AND SUPPRESSES NEUROINFLAMMATION

ACTIVATED MICROGLIA
Pro-inflammatory phenotype

Amoeboid shape
Highly activated microglia

NF-κB PATHWAY
IκBα — P
NF-κB
TRANSCRIPTION ACTIVATED

PRO-INFLAMMATORY CYTOKINES
↑ TNF-α ↑ IL-1β ↑ IL-6

H_2S

- Reduces neuroinflammation
- Protects neurons
- Preserves synaptic function
- Slows disease progression

INHIBITED MICROGLIA
Anti-inflammatory phenotype

NF-κB PATHWAY
IκBα
NF-κB
TRANSCRIPTION SUPPRESSED

PRO-INFLAMMATORY CYTOKINES
↓ TNF-α ↓ IL-1β ↓ IL-6

Ramified shape
Resting microglia

H_2S SUPPRESSES NEUROINFLAMMATION AND PROTECTS THE BRAIN

pharmaceuticals
MDPI
Review

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

Constantin Munteanu [1,2,*], Anca Irina Galaction [1], Gelu Onose [2,3], Marius Turnea [1,*] and Mariana Rotariu [1]

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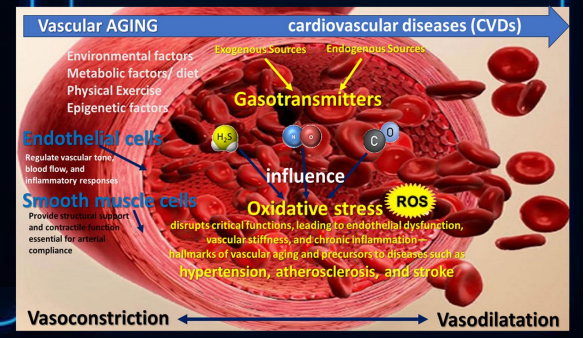
Abstract: Age-related oxidative stress is a critical factor in vascular dysfunction, contributing to hypertension and atherosclerosis. Smooth muscle cells and endothelial cells are particularly susceptible to oxidative damage, which exacerbates vascular aging through cellular senescence, chronic inflammation, and arterial stiffness. Gasotransmitters—hydrogen sulfide (H_2S), 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 H_2S, NO, and CO influence vascular smooth muscle and endothelial cell function. Therapeutic strategies involving exogenous gasotransmitter delivery systems and combination therapies were analyzed. H_2S 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

1. Introduction



Neuroinflammation is increasingly recognized as a driver of neurodegenerative progression. H_2S may influence microglial activation and cytokine production, including TNF-α, IL-1β, and IL-6. Rather than completely suppressing inflammation, H_2S appears to modulate inflammatory responses and promote a more balanced neuroimmune environment.

PILLAR 4:
PROTEIN HOMEOSTASIS

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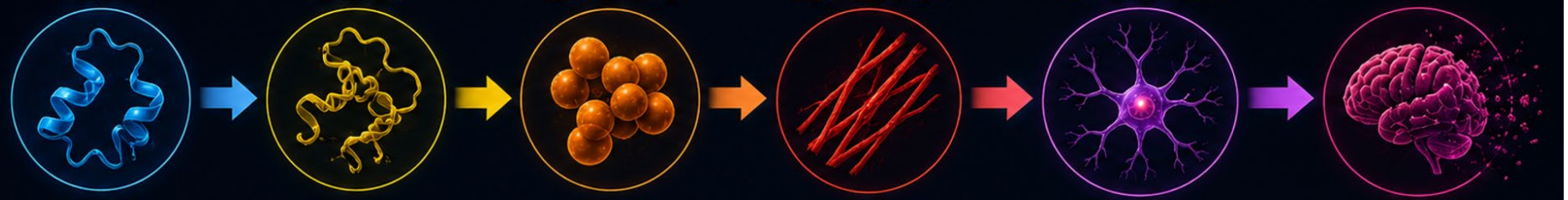
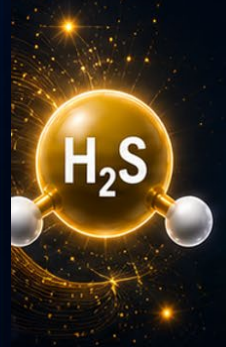
NEUROLOGY AND NEUROLOGICAL DISORDERS

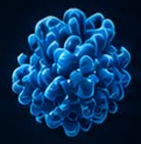
H_2S MAINTAINS PROTEIN HOMEOSTASIS AND PREVENTS TOXIC AGGREGATION

PROTEIN AGGREGATION CASCADE



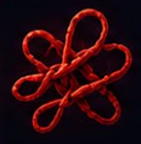
KEY PATHOLOGICAL PROTEINS



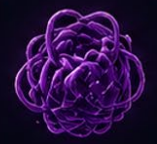


AMYLOID-β
Plaque formation (Alzheimer's disease)

TAU
Neurofibrillary tangles (Alzheimer's disease)



α-SYNUCLEIN
Lewy body formation (Parkinson's disease)



TDP-43
Pathological inclusions (ALS, FTLD)

H_2S PRESERVES PROTEIN HOMEOSTASIS AND PROTECTS THE BRAIN

International Journal of Molecular Sciences — MDPI

Review

Recent Advances in Molecular Research on Hydrogen Sulfide (H_2S) Role in Diabetes Mellitus (DM)—A Systematic Review

Constantin Munteanu [1,2,*], Mariana Rotariu [1], Marius Turnea [1], Gabriela Dogaru [3,4], Cristina Popescu [2], Aura Spinu [2,5], Ioana Andone [2,5], Ruxandra Postoiu [2], Elena Valentina Ionescu [6,7], Carmen Oprea [6,7], Irina Albadi [6,8] and Gelu Onose [2,5,*]

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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 (H_2S) Role in Diabetes Mellitus (DM)—A Systematic Review. *Int. J. Mol. Sci.* **2022**, *23*, 6720. https://doi.org/10.3390/ijms23126720

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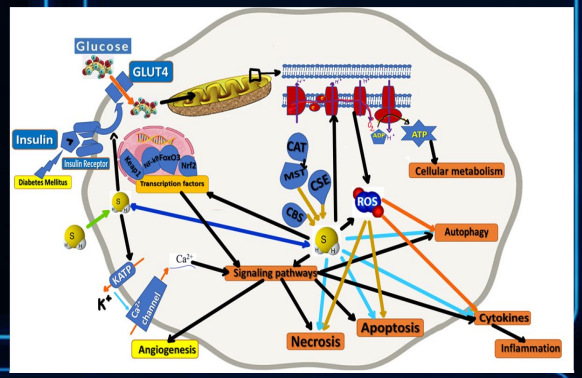
Abstract: Abundant experimental data suggest that hydrogen sulfide (H_2S) is related to the pathophysiology of Diabetes Mellitus (DM). Multiple molecular mechanisms, including receptors, membrane ion channels, signalingmolecules, enzymes, and transcription factors, are known to be responsible for the H_2S biological actions; however, H_2S 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 H_2S have been identified, either based on H_2S exogenous upport 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 H_2S 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 H_2S 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 H_2S as a therapeutic agent is still at the beginning.

Keywords: hydrogen sulfide (H_2S); 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



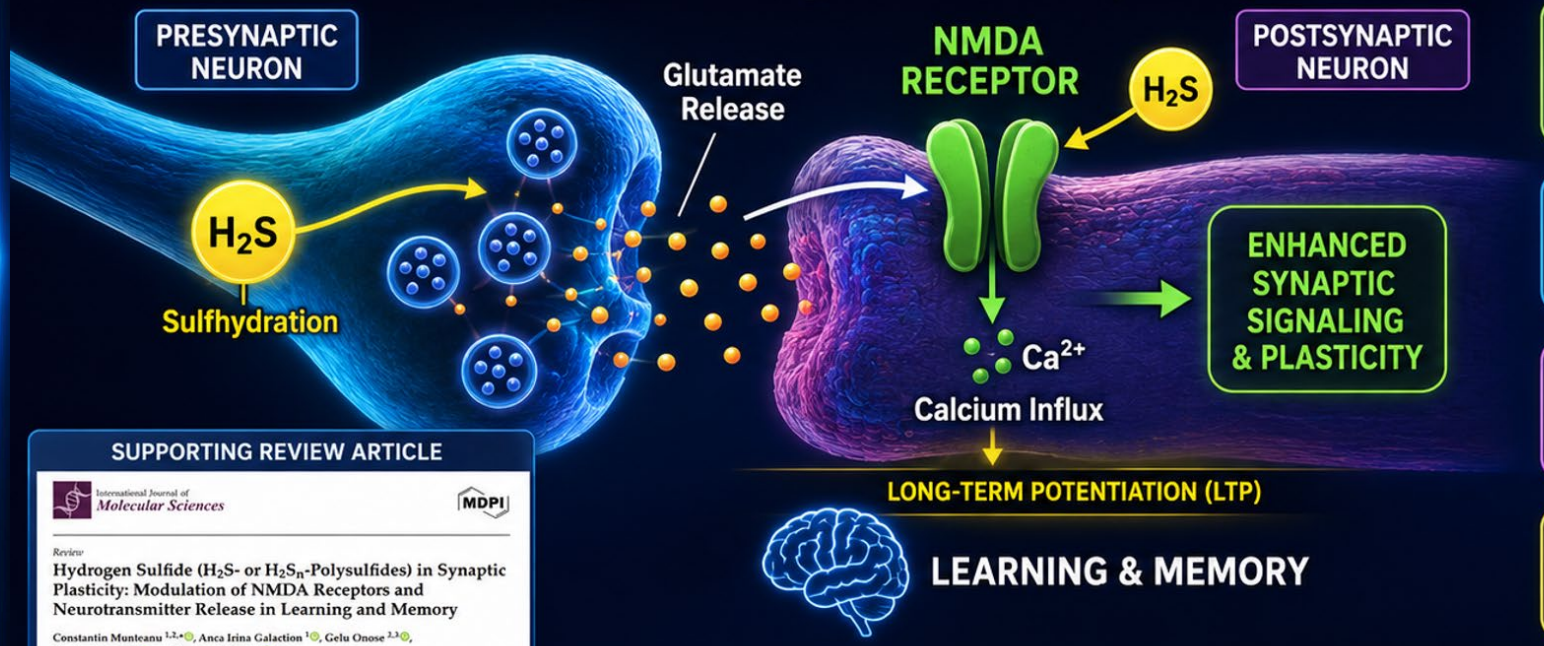
Protein aggregation is a defining feature of many neurodegenerative diseases. Amyloid-β, tau, α-synuclein, and TDP-43 accumulate when proteostasis mechanisms fail. Current evidence suggests that H_2S may influence protein folding, autophagy, and proteasomal activity, thereby contributing to the maintenance of protein homeostasis.

SLIDE 9

Pillar 5: Synaptic Plasticity

H_2S modulates NMDA receptors and supports learning, memory, and neuroplasticity

NEURO CONCLAVE 2026
ADVANCING BRAIN HEALTH TOGETHER



NMDA RECEPTORS

LEARNING

MEMORY

NEUROPLASTICITY

SUPPORTING REVIEW ARTICLE

International Journal of Molecular Sciences — MDPI

Review

Hydrogen Sulfide (H_2S- or H_2S_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]

International Journal of Molecular Sciences — MDPI

Review

Hydrogen Sulfide (H_2S- or H_2S_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]

1 Department of Biomedical Sciences, Faculty of Medical Bioengineering, University of Medicine and Pharmacy "Grigore T. Popa", 700454 Iasi, Romania; anca.galaction@umfiasi.ro (A.I.G.); mariana.rotariu@umfiasi.ro (M.R.)
2 Neuromuscular Rehabilitation Clinic Division, Clinical Emergency Hospital "Bagdasar-Arseni", 041915 Bucharest, Romania; gelu.onose@umfcd.ro
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Abstract: Hydrogen sulfide (H_2S) 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 H_2S regulates NMDA receptor function and neurotransmitter release in neuronal circuits. By synthesizing findings from animal and cellular models, we investigate the impacts of enzymatic H_2S production and exogenous H_2S on excitatory synaptic currents, long-term potentiation, and intracellular calcium signaling. Data suggest that H_2S interacts directly with NMDA receptor subunits, altering receptor function and modulating neuronal excitability. Simultaneously, H_2S promotes the release of neurotransmitters such as glutamate and GABA, shaping synaptic dynamics and plasticity. Furthermore, reports indicate that disruptions in H_2S metabolism contribute to cognitive impairments and neurodegenerative disorders, underscoring the potential therapeutic value of targeting H_2S-mediated pathways. Although the precise mechanisms of H_2S-induced changes in synaptic strength remain elusive, a growing body of evidence positions H_2S as a significant regulator of memory formation processes. This review calls for more rigorous exploration into the molecular underpinnings of H_2S in synaptic plasticity, paving the way for novel pharmacological interventions in cognitive dysfunction.

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

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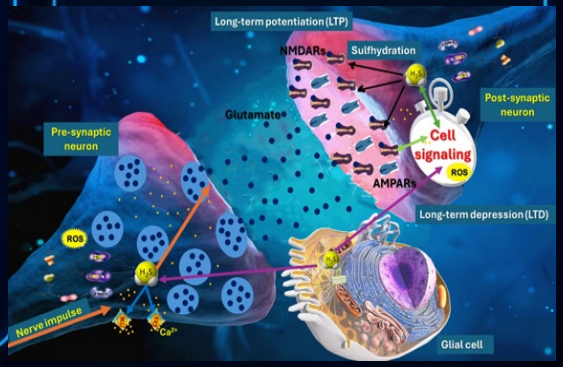


H_2S SUPPORTS SYNAPTIC PLASTICITY AND MAY IMPROVE COGNITIVE RESILIENCE.

H_2S is strongly linked to synaptic plasticity. Experimental studies demonstrate modulation of NMDA receptor activity, neurotransmitter release, calcium signaling, and long-term potentiation. These mechanisms place H_2S at the intersection between molecular signaling and higher-order functions such as learning, memory, and cognitive resilience.

ALZHEIMER'S DISEASE

THE H_2S–AD CASCADE

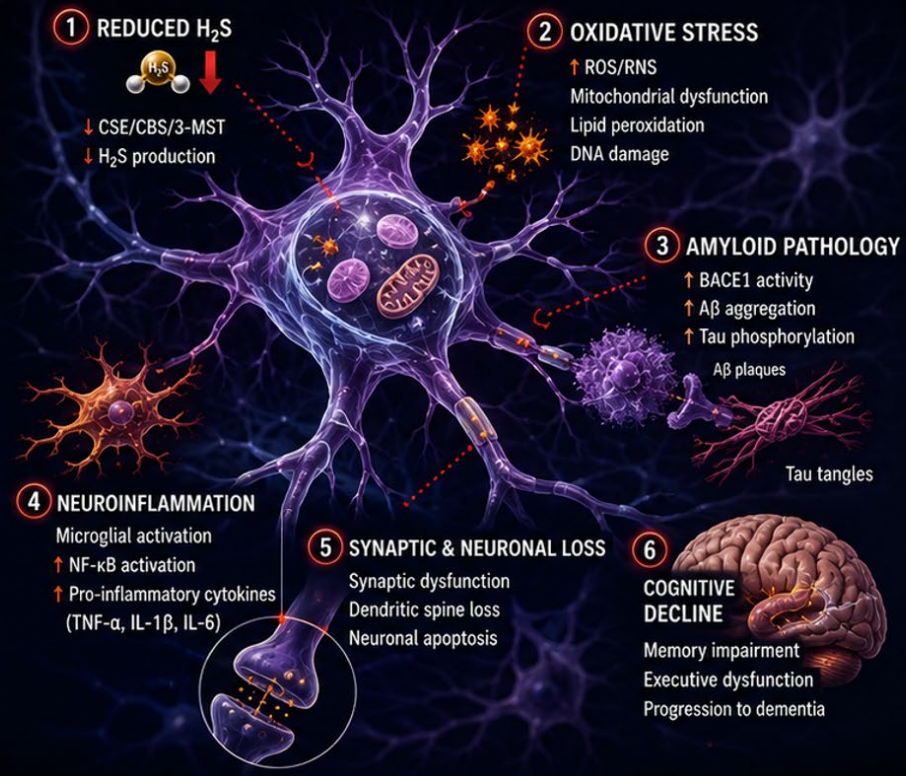
REDUCED H_2S
↓ CSE/CBS/3-MST
↓ H_2S production

OXIDATIVE STRESS
↑ ROS • Mitochondrial dysfunction
↓ Antioxidant defenses (Nrf2)

AMYLOID PATHOLOGY
↑ Aβ production & aggregation
↑ Tau hyperphosphorylation
↑ Neuroinflammation

COGNITIVE DECLINE
Synaptic loss • Neuronal death
Memory impairment • Dementia

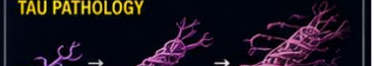
HOW REDUCED H_2S DRIVES THE ALZHEIMER'S CASCADE



1. **REDUCED H_2S**
   ↓ CSE/CBS/3-MST
   ↓ H_2S production
2. **OXIDATIVE STRESS**
   ↑ ROS/RNS
   Mitochondrial dysfunction
   Lipid peroxidation
   DNA damage
3. **AMYLOID PATHOLOGY**
   ↑ BACE1 activity
   ↑ Aβ aggregation
   ↑ Tau phosphorylation
   Aβ plaques
   Tau tangles
4. **NEUROINFLAMMATION**
   Microglial activation
   ↑ NF-κB activation
   ↑ Pro-inflammatory cytokines (TNF-α, IL-1β, IL-6)
5. **SYNAPTIC & NEURONAL LOSS**
   Synaptic dysfunction
   Dendritic spine loss
   Neuronal apoptosis
6. **COGNITIVE DECLINE**
   Memory impairment
   Executive dysfunction
   Progression to dementia

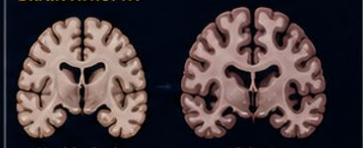
Aβ AGGREGATION

TAU PATHOLOGY



SYNAPTIC DYSFUNCTION

BRAIN ATROPHY



H_2S DEFICIENCY INDUCES OXIDATIVE STRESS, PROMOTES AMYLOID/Tau PATHOLOGY, AND DRIVES NEURODEGENERATION IN **ALZHEIMER'S DISEASE**

Sources: Munteanu C. et al.
Mechanistic Intimate Insights into the Role of Hydrogen Sulfide in Alzheimer's Disease: A Recent Systematic Review.
International Journal of Molecular Sciences. 2023; 24(10): 8744.

NEURO CONCLAVE 2026
NEUROLOGY AND NEUROLOGICAL DISORDERS

International Journal of Molecular Sciences
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Review

Mechanistic Intimate Insights into the Role of Hydrogen Sulfide in Alzheimer's Disease: A Recent Systematic Review

Constantin Munteanu [1,2,*], Mihail Hoteteu [2], Cristina Popescu [2,3,*], Ruxandra Postoiu [3], Andrei Iordan [4], Ilie Onu [3] and Gelu Onose [2,3]

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Abstract: In the rapidly evolving field of Alzheimer's Disease (AD) research, the intricate role of Hydrogen Sulfide (H_2S) has garnered critical attention for its diverse involvement in both pathological substrates and prospective therapeutic paradigms. While conventional pathophysiological models of AD have primarily emphasized the significance of amyloid-beta (Aβ) deposition and tau protein hyperphosphorylation, this targeted systematic review meticulously aggregates and rigorously appraises seminal contributions from the past year elucidating the complex mechanisms of H_2S in AD pathogenesis. Current scholarly literature accentuates H_2S's dual role, delineating its regulatory functions in critical cellular processes—such as neurotransmission, inflammation, and oxidative stress homeostasis—while concurrently highlighting its disruptive impact on quintessential AD biomarkers. Moreover, this review illuminates the nuanced mechanistic intimate interactions of H_2S in cerebrovascular and cardiovascular pathology associated with AD, thereby exploring avant-garde therapeutic modalities, including sulfurous mineral water inhalations and mud therapy. By emphasizing the potential for therapeutic modulation of H_2S via both donors and inhibitors, this review accentuates the imperative for future research endeavors to deepen our understanding, thereby potentially advancing novel diagnostic and therapeutic strategies in AD.

Keywords: Alzheimer's Disease; Hydrogen Sulfide (H_2S); Amyloid-beta (Aβ) Aggregation; Tau Hyperphosphorylation; Cellular Homeostasis; Neuroinflammation; Neuroprotection

Citation: To be added by editorial staff during production.
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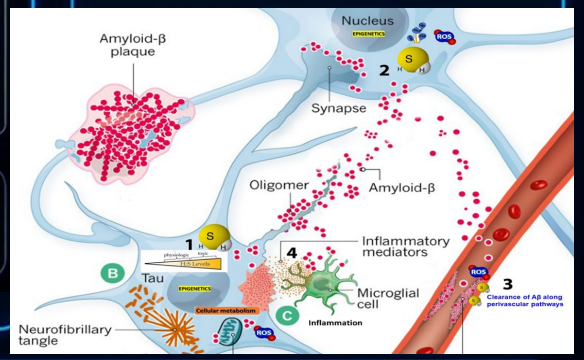
1. Introduction

Alzheimer's Disease (AD), the predominant version of dementia, imposes a substantial public health burden [1], afflicting an estimated 50 million individuals globally [2].



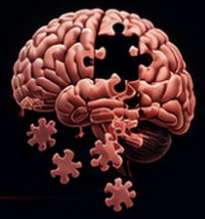
In Alzheimer's disease, reduced H_2S bioavailability has been associated with oxidative stress, mitochondrial dysfunction, amyloid accumulation, and progressive cognitive decline. Although causality remains under investigation, multiple observations suggest that altered sulfur signaling may contribute to disease progression.

H_2S AND ALZHEIMER'S DISEASE: THE IMPORTANCE OF HOMEOSTASIS

H_2S IS BENEFICIAL ONLY WITHIN A PHYSIOLOGICAL RANGE – BOTH DEFICIENCY AND EXCESS CAN BE HARMFUL

TOO LITTLE H_2S

- Impaired signaling
- Increased oxidative stress
- Mitochondrial dysfunction
- Neuroinflammation
- Enhanced AD pathology



TOO MUCH H_2S

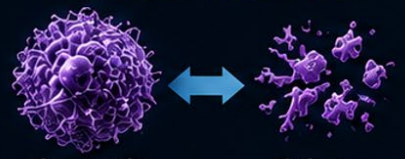
- Oxidative/nitrosative stress
- Mitochondrial inhibition
- Protein sulfhydration excess
- Neuroinflammation
- Potential neurotoxicity

PHYSIOLOGICAL H_2S HOMEOSTASIS

Balanced redox state • Mitochondrial support • Controlled inflammation
Synaptic function • Neuronal survival

1 AMYLOID-β

Physiological H_2S may influence

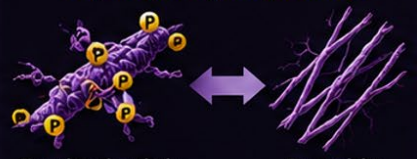


Aβ aggregation ⟷ Aβ clearance

May reduce Aβ aggregation and support Aβ clearance

2 TAU

Physiological H_2S may modulate



Tau phosphorylation ⟷ Tau toxicity

May modulate tau phosphorylation and reduce tau toxicity

3 MITOCHONDRIA

Physiological H_2S supports

Damaged mitochondrion ⟷ Healthy mitochondrion

- ↑ ATP production
- ↑ Biogenesis
- ↓ ROS
- ↓ mPTP opening

Supports mitochondrial function, but excessive H_2S may inhibit respiration and impair bioenergetics

4 COGNITION

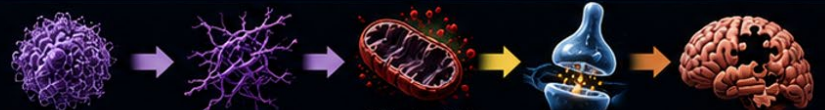
Physiological H_2S may be associated with

- ✓ Synaptic plasticity
- ✓ Learning
- ✓ Memory
- ? Neuroplasticity (potential)

May support synaptic plasticity, learning and memory – human evidence remains limited and inconclusive

H_2S HOMEOSTASIS IS KEY:

NEITHER DEFICIENCY NOR EXCESS IS DESIRABLE.



MAINTAINING PHYSIOLOGICAL H_2S LEVELS MAY HELP PRESERVE NEURONAL HEALTH IN ALZHEIMER'S DISEASE.

International Journal of Molecular Sciences
MDPI

Review

The Role of Hydrogen Sulfide (H_2S) in Epigenetic Regulation of Neurodegenerative Diseases: A Systematic Review

Bombonica Gabriela Dogaru [1,2] and Constantin Munteanu [3,4,*]

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Abstract: This review explores the emerging role of hydrogen sulfide (H_2S) in modulating epigenetic mechanisms involved in neurodegenerative diseases. Accumulating evidence has begun to elucidate the multifaceted ways in which H_2S influences the epigenetic landscape and, subsequently, the progression of various neurodegenerative disorders, including Alzheimer's, Parkinson's, and Huntington's disease. H_2S 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 H_2S 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 H_2S levels or its downstream targets. We conclude by identifying future directions for research aimed at exploiting the therapeutic potential of H_2S 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

Citation: Dogaru, B.G.; Munteanu, C. The Role of Hydrogen Sulfide (H_2S) in Epigenetic Regulation of Neurodegenerative Diseases: A Systematic Review. *Int. J. Mol. Sci.* 2023, 24, x. https://doi.org/10.3390/xxxxx

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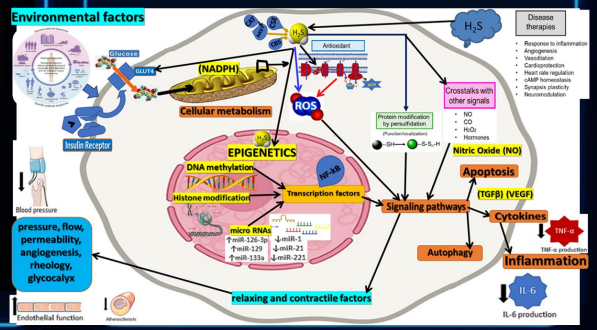
1. Introduction

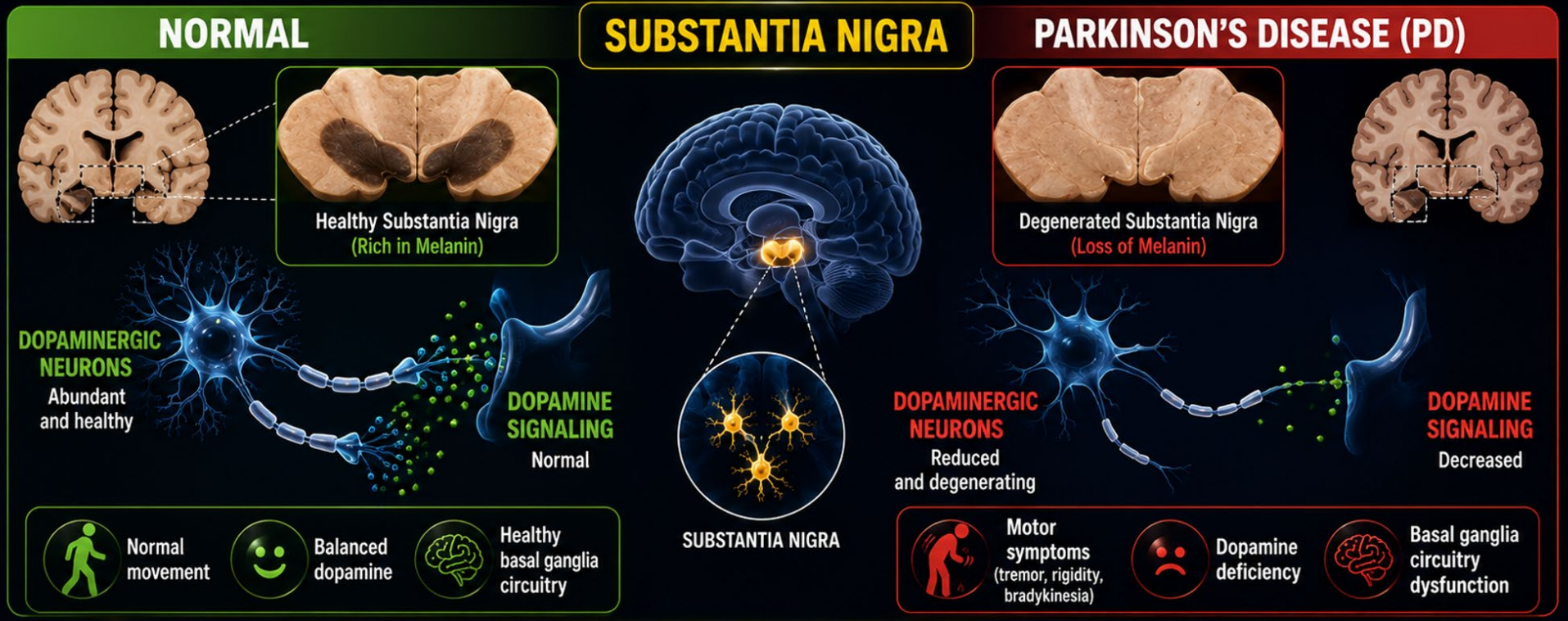
Neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's, pose a formidable challenge in modern medicine [1,2]. These conditions are characterized by the relentless and irreversible loss of neurons, leading to a gradual decline in cognitive and motor functions [3]. They have become 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].



A key message is that H_2S biology follows a homeostatic model. Both deficiency and excess may be harmful. Physiological signaling appears to support mitochondrial function, synaptic activity, and redox balance, whereas disruption of this equilibrium may contribute to neurodegeneration. Therefore, the objective is not maximal H_2S exposure but optimal H_2S homeostasis.

PARKINSON'S DISEASE

LOSS OF DOPAMINERGIC NEURONS



PARKINSON'S DISEASE IS CHARACTERIZED BY THE PROGRESSIVE LOSS OF DOPAMINERGIC NEURONS IN THE SUBSTANTIA NIGRA

nutrients

MDPI

Review

Actual Data on Essential Trace Elements in Parkinson's Disease

Cristina Popescu [1,2], Constantin Munteanu [2,3,*], Aura Spînu [1,2], Ioana Andone [1,2], Roxana Bistriceanu [1,2], Ruxandra Postoiu [1,2], Andreea Suciu [1,2], Sebastian Giuvara [1,2], Andreea-Iulia Vlădulescu-Trandafir [1,2], Sorina Maria Aurelian [1,4], Nadina Liana Pop [5], Vlad Ciobanu [6] and Gelu Onose [1,2]

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Abstract: *"Sola dosis facit venenum"* (Paracelsus). Essential trace elements, crucial for maintaining neuronal function, have their dysregulation increasingly correlated with neurodegenerative disorders, particularly Parkinson's disease (PD). This systematic review aims to synthesize recent high-quality evidence regarding the involvement of essential trace elements, such as iron, zinc, copper, manganese, and selenium, in the pathogenesis and, consequently, as potential therapeutic targets of PD. A comprehensive literature search was conducted for articles published between 1 January 2023 and 31 December 2024. Out of an initial pool of 1231 identified studies, 63 met the methodological eligibility criteria according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. All potentially eligible interventional and observational studies were initially assessed using the Physiotherapy Evidence Database (PEDro) scale, which is commonly employed for evaluating the internal validity and statistical interpretability of clinical trials and rehabilitation-focused studies. Following the qualitative assessment using the PEDro scale, 18 studies were ultimately selected based on their scientific relevance and methodological rigor. To supplement the PEDro scoring, which is designed primarily for individual trials, we applied the AMSTAR-2 (A MeaSurement Tool to Assess Systematic Reviews) checklist for the evaluation of the included systematic reviews or meta-analyses. The included studies employed a variety of clinical, postmortem, and experimental models to investigate trace-element concentrations and their mechanistic roles in PD. The findings revealed consistent patterns of iron accumulation in the substantia nigra, zinc's bidirectional effects on oxidative stress and autophagy, copper-induced α-synuclein aggregation, and the neuroprotective role of selenium via antioxidant pathways. Manganese was associated with mitochondrial dysfunction and neuroinflammation. Essential trace-element disturbances contribute to PD pathology through interconnected mechanisms involving redox imbalance, protein misfolding, and impaired cellular homeostasis. These elements may serve as both biomarkers and potential therapeutic tools, warranting further investigation into personalized metal-based interventions for PD.

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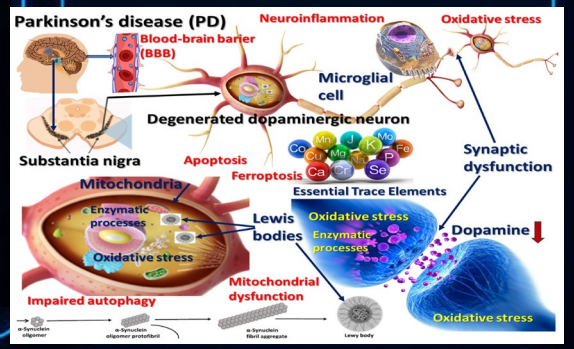

Parkinson's disease is characterized by progressive loss of dopaminergic neurons in the substantia nigra. Oxidative stress, mitochondrial dysfunction, and neuroinflammation all participate in this process. These mechanisms overlap remarkably with the biological pathways regulated by H_2S.

H_2S AND DOPAMINERGIC PROTECTION

PHYSIOLOGICAL H_2S SIGNALING MAY MODULATE KEY PATHWAYS INVOLVED IN DOPAMINERGIC NEURON VULNERABILITY

OXIDATIVE STRESS

- ROS / RNS
- Redox imbalance
- Protein oxidation
- Lipid peroxidation

ROS RNS

INCREASES NEURON VULNERABILITY

MITOCHONDRIAL DYSFUNCTION

- Complex I dysfunction
- ↓ ATP production
- Impaired bioenergetics
- Mitophagy imbalance

INCREASES NEURON VULNERABILITY

NEUROINFLAMMATION

- Microglial activation
- NF-κB activation
- ↑ Pro-inflammatory cytokines (TNF-α, IL-1β, IL-6)
- Chronic inflammation

INCREASES NEURON VULNERABILITY

APOPTOSIS

- Mitochondrial (intrinsic) pathway activation
- Caspase activation
- DNA damage
- Cell death signaling

INCREASES NEURON VULNERABILITY

H_2S

PHYSIOLOGICAL H_2S SIGNALING

DOPAMINERGIC NEURON

TOO LITTLE H_2S
Impaired signaling
Higher vulnerability

HOMEOSTASIS

TOO MUCH H_2S
Sulfide toxicity
Higher vulnerability

PHYSIOLOGICAL H_2S SIGNALING MAY INFLUENCE MULTIPLE MECHANISMS INVOLVED IN DOPAMINERGIC NEURON DEGENERATION.

CONCENTRATION
CONTEXT
DISEASE STAGE
MATTER

International Journal of Molecular Sciences
MDPI

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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† These authors contributed equally to this work.

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

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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/ijms252011272

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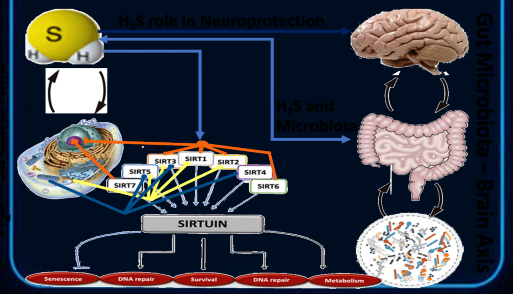


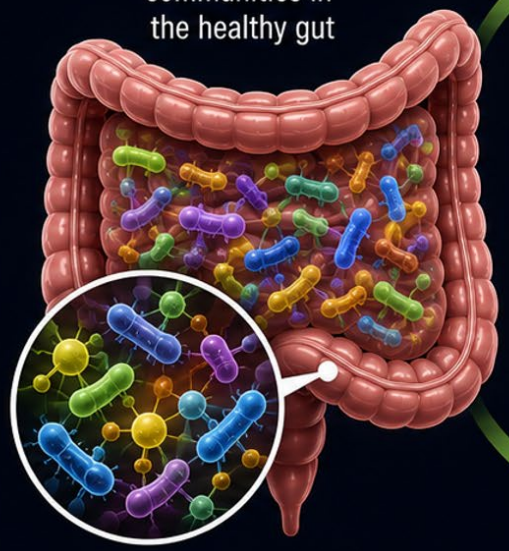
Rather than viewing H_2S as a cure, it is more accurate to view it as a modulator of neuronal vulnerability. Physiological H_2S signaling may influence oxidative stress, mitochondrial integrity, inflammatory responses, and apoptosis. Importantly, these effects are context-dependent and strongly influenced by concentration and disease stage.

GUT–BRAIN–H_2S AXIS

MICROBIOTA-DERIVED H_2S LINKS GUT FUNCTION AND BRAIN HEALTH

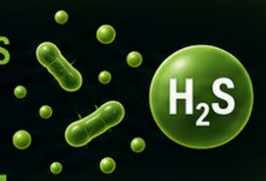
1. GUT MICROBIOTA

Diverse microbial communities in the healthy gut



2. MICROBIAL H_2S

Microbial production of hydrogen sulfide



3. BRAIN

H_2S signaling reaches the brain and modulates multiple pathways

H_2S ACTIONS IN THE BRAIN

Neuroprotection
Reduces oxidative stress and neuronal injury

Anti-inflammatory
Modulates microglial activation and neuroinflammation

Redox balance
Restores redox homeostasis and antioxidant defenses

Mitochondrial support
Improves mitochondrial function and bioenergetics

Synaptic plasticity and cognition
Supports synaptic function, learning and memory

The gut microbiota produces H_2S that reaches the brain and may influence multiple pathways involved in neuroprotection and brain health.

biomedicines

MDPI

Review

Role of Microbiota-Derived Hydrogen Sulfide (H_2S) in Modulating the Gut–Brain Axis: Implications for Alzheimer's and Parkinson's Disease Pathogenesis

Constantin Munteanu [1,2,*], Gelu Onose [2,3], Mariana Rotariu [1,*], Mădălina Poștaru [1], Marius Turnea [1] and Anca Irina Galaction [1]

[1] Department of Biomedical Sciences, Faculty of Medical Bioengineering, University of Medicine and Pharmacy "Grigore T. Popa", 700454 Iasi, Romania; madalina.postaru@umfiasi.ro (M.P.); marius.turnea@umfiasi.ro (M.T.); anca.galaction@umfiasi.ro (A.I.G.)
[2] Neuromuscular Rehabilitation Clinic Division, Clinical Emergency Hospital "Bagdasar-Arseni", 041915 Bucharest, Romania; gelu.onose@umfcd.ro
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* Correspondence: constantin.munteanu.biolog@umfiasi.ro (C.M.); mariana.rotariu@umfiasi.ro (M.R.)

Abstract: Microbiota-derived hydrogen sulfide (H_2S) plays a crucial role in modulating the gut–brain axis, with significant implications for neurodegenerative diseases such as Alzheimer's and Parkinson's. H_2S is produced by sulfate-reducing bacteria in the gut and acts as a critical signaling molecule influencing brain health via various pathways, including regulating inflammation, oxidative stress, and immune responses. H_2S maintains gut barrier integrity at physiological levels and prevents systemic inflammation, which could impact neuroinflammation. However, as H_2S has a dual role or a Janus face, excessive H_2S production, often resulting from gut dysbiosis, can compromise the intestinal barrier and exacerbate neurodegenerative processes by promoting neuroinflammation and glial cell dysfunction. This imbalance is linked to the early pathogenesis of Alzheimer's and Parkinson's diseases, where the overproduction of H_2S exacerbates beta-amyloid deposition, tau hyperphosphorylation, and alpha-synuclein aggregation, driving neuroinflammatory responses and neuronal damage. Targeting gut microbiota to restore H_2S homeostasis through dietary interventions, probiotics, prebiotics, and fecal microbiota transplantation presents a promising therapeutic approach. By rebalancing the microbiota-derived H_2S, these strategies may mitigate neurodegeneration and offer novel treatments for Alzheimer's and Parkinson's diseases, underscoring the critical role of the gut–brain axis in maintaining central nervous system health.

Keywords: microbiota; dysbiosis; H_2S; gut–brain axis; Alzheimer's disease; Parkinson's disease; glial cell dysfunction; neuroinflammation; neurodegeneration; probiotics; prebiotics

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Citation: Munteanu, C.; Onose, G.; Rotariu, M.; Poștaru, M.; Turnea, M.; Galaction, A.I. Role of Microbiota-Derived Hydrogen Sulfide (H_2S) in Modulating the Gut–Brain Axis: Implications for Alzheimer's and Parkinson's Disease Pathogenesis. *Biomedicines* **2024**, *12*, 2670. https://doi.org/10.3390/biomedicines12122670

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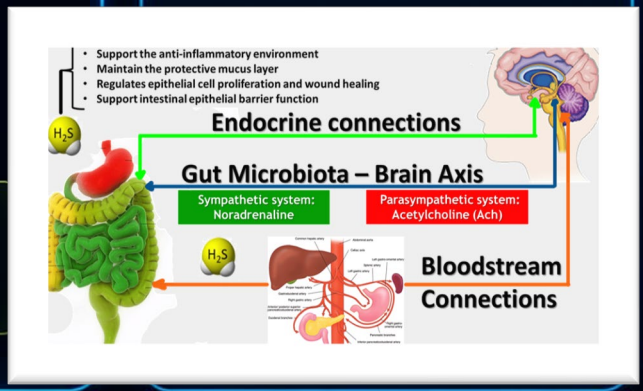
1. Introduction

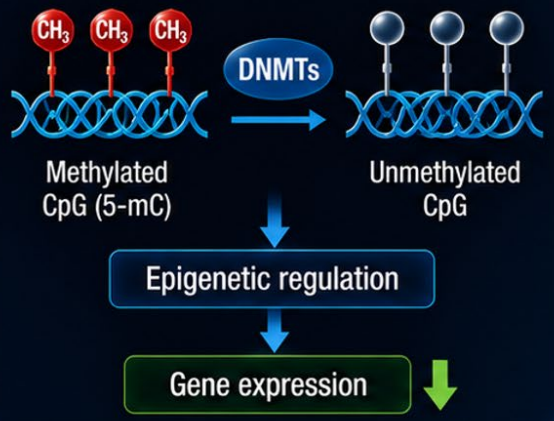
The human gastrointestinal (GI) tract harbors a complex community of trillions of microorganisms, including bacteria, archaea, fungi, and viruses, collectively referred to as the gut microbiota [1]. These microorganisms are crucial for maintaining homeostasis and performing essential functions such as digestion, nutrient absorption, immune system regulation, and the maintenance of the intestinal barrier [2]. In recent years, a growing body of



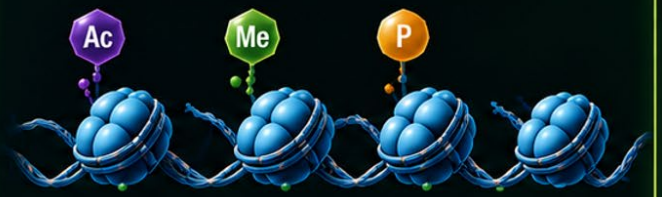
The gut microbiota has emerged as a major source of biologically active sulfur metabolites. Microbial H_2S may influence systemic physiology and brain function through multiple signaling pathways. This gut–brain–H_2S axis represents one of the most rapidly expanding research areas in neurodegeneration.

EPIGENETIC REGULATION

1. DNA METHYLATION



2. HISTONE MODIFICATION



- Acetylation
- Methylation
- Phosphorylation
- Chromatin remodeling

Transcriptional control

Gene expression

3. NON-CODING RNAs

Post-transcriptional regulation

Gene expression

- CH3 DNA methylation (5-mC)
- Ac Histone acetylation
- Me Histone methylation
- P Histone phosphorylation

International Journal of Molecular Sciences

MDPI

Review

The Role of Hydrogen Sulfide (H_2S) in Epigenetic Regulation of Neurodegenerative Diseases: A Systematic Review

Bombonica Gabriela Dogaru [1,2] and Constantin Munteanu [3,4,*]

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

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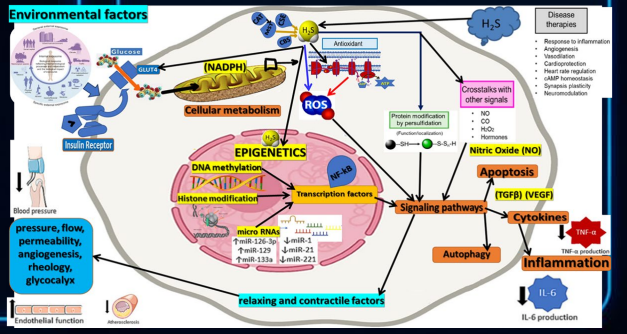
1. Introduction

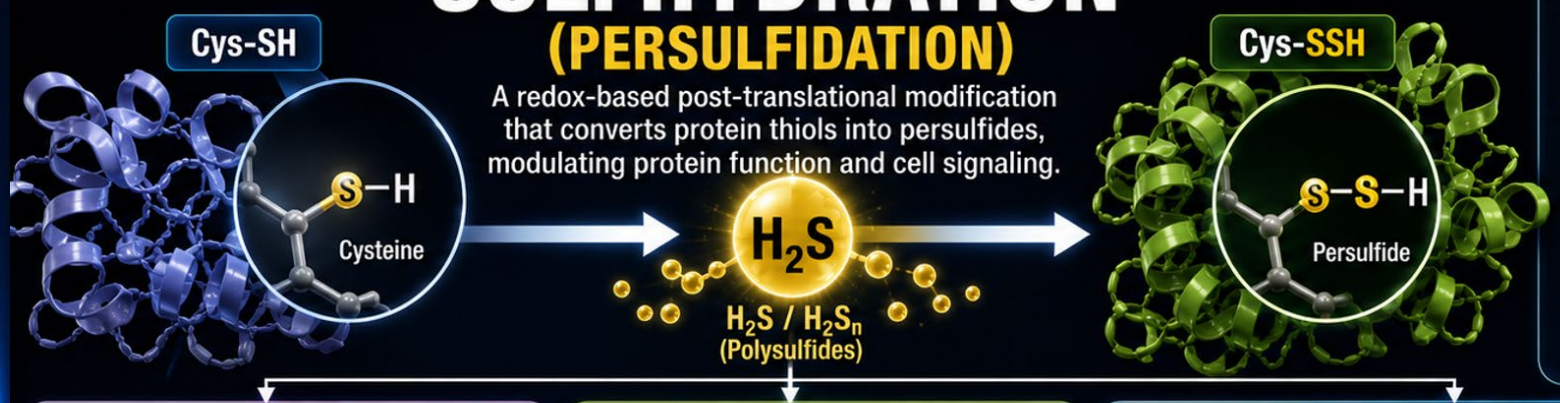
Neurodegenerative diseases, including Alzheimer's, Parkinson's, and Huntington's, pose a formidable challenge in modern medicine [1,2]. These conditions are characterized by the relentless and irreversible loss of neurons, leading to a gradual decline in cognitive and motor functions [3]. They have become 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].



H_2S may also influence epigenetic regulation. Current evidence suggests interactions with DNA methylation, histone modifications, and non-coding RNAs. These mechanisms provide a potential bridge between environmental exposures, microbiota-derived metabolites, and long-term regulation of neuronal gene expression.

SULFHYDRATION
(PERSULFIDATION)

A redox-based post-translational modification that converts protein thiols into persulfides, modulating protein function and cell signaling.



PERSULFIDATION

- Addition of one or more sulfur atom(s) to a cysteine thiol (Protein-SH)
- Reversible modification sensitive to the cellular redox environment

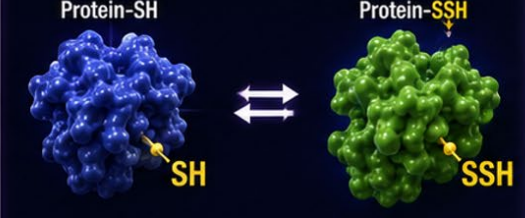
REVERSIBLE SWITCH

Reducing systems (Trx, Grx, GSH)

⟷

Oxidative / Nitrosative stress

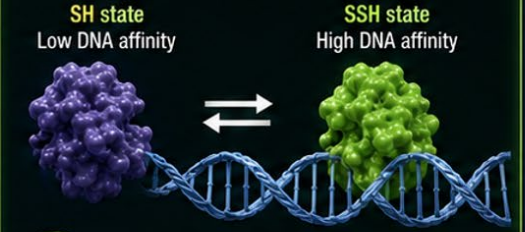
1. PROTEIN FUNCTION



Conformational change

Altered enzyme activity, localization, stability and protein–protein interactions

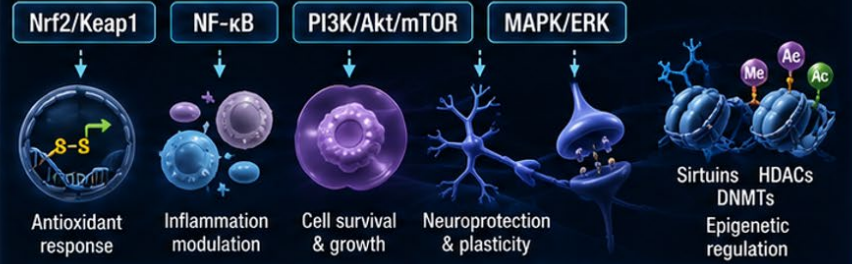
2. TRANSCRIPTION FACTORS



Regulation of DNA binding and gene expression

Activation or repression of target genes

3. CELL SIGNALING & EPIGENETICS



Fine-tuning of signaling pathways and epigenetic regulators

MOLECULAR SWITCH

Protein-SH (Inactive / Basal state) ⟷ SULFHYDRATION / DESULFHYDRATION ⟷ Protein-SSH (Active / Modified state)

- Dynamic and reversible
- Context-dependent
- Essential for redox signaling and cellular homeostasis

BIOLOGICAL OUTCOMES

- Redox homeostasis
- Stress adapendent
- Inflammation control
- Metabolism regulation
- Cell survival & protection

pharmaceuticals MDPI

Review

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

Constantin Munteanu [1,2,*], Anca Irina Galaction [1], Gelu Onose [2,3], Marius Turnea [1,*] and Mariana Rotariu [1]

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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 (H_2S), 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 H_2S, NO, and CO influence vascular smooth muscle and endothelial cell function. Therapeutic strategies involving exogenous gasotransmitter delivery systems and combination therapies were analyzed. H_2S 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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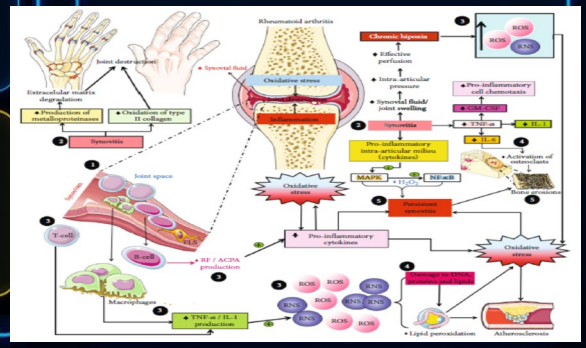
1. Introduction



Perhaps the most distinctive mechanism of H_2S biology is sulfhydration, also known as persulfidation. This reversible post-translational modification converts protein thiols into persulfides, altering protein activity, transcription factor behavior, and cellular signaling. Increasingly, persulfidation is viewed as a fundamental mechanism of H_2S-mediated biological regulation.

THERAPEUTIC OPPORTUNITIES

THE FUTURE H_2S THERAPEUTIC ROADMAP

1. H_2S DONORS

- Small molecules (e.g., NaHS, GYY4137)
- Slow-release & mitochondria-targeted
- Prodrugs & smart nanocarriers
- Controlled H_2S delivery

2. NUTRITION

- Sulfur-rich foods
- Boost endogenous H_2S production
- Synergy with polyphenols
- Personalized dietary strategies

H_2S
HEALTH & HOMEOSTASIS

3. MICROBIOTA MODULATION

- Support H_2S-producing bacteria
- Prebiotics, probiotics, synbiotics
- Restore gut–brain–immune axis
- Improve barrier and metabolism

4. PRECISION MEDICINE

- Biomarkers for H_2S pathways
- Genetic, epigenetic & metabolomic profiling
- Patient stratification
- Tailored H_2S–based therapies

REDUCE OXIDATIVE STRESS AND INFLAMMATION

ENHANCE MITOCHONDRIAL FUNCTION

FROM MOLECULAR INSIGHTS TO PERSONALIZED HEALTH

SUPPORT NEUROPROTECTION AND GUT–BRAIN AXIS

PERSONALIZED THERAPIES MAXIMIZE BENEFIT

SAFETY • EFFICACY • PRECISION • LONGEVITY

BETTER OUTCOMES FOR CHRONIC DISEASES AND HEALTHSPAN

Several therapeutic strategies are currently being explored. These include H_2S-releasing compounds, nutritional interventions, microbiota modulation, and precision medicine approaches guided by biomarkers. While clinical translation remains at an early stage, the field is rapidly evolving.

H_2S-CENTERED MODEL OF NEURODEGENERATION

A SYSTEMS BIOLOGY NETWORK IN NEURODEGENERATION

REDOX HOMEOSTASIS

Antioxidant
- ↑ GSH
- ↑ Trx
- ↑ SOD
- ↑ Catalase

ROS — RNS

Anti-inflammatory
- ↓ ROS
- ↓ RNS
- ↓ Oxidative Stress

Redox signaling & cellular protection

MITOCHONDRIAL HOMEOSTASIS

- Enhance ATP production
- Preserve mitochondrial membrane potential
- Reduce mitochondrial ROS
- Promote mitophagy and biogenesis
- Prevent cytochrome c release

Fission ↔ Fusion

Energy Metabolism

RESULTS

- Neuronal survival
- Synaptic plasticity
- Cognitive function
- Healthy aging

PROTEOSTASIS

- Promote protein folding
- Enhance chaperone function (HSPs)
- Reduce protein aggregation (Aβ, Tau, α-synuclein)
- Activate autophagy and proteasome

Protein folding
Autophagy
Proteasome

SIGNALING PATHWAYS

Nrf2/ARE | PI3K/Akt | AMPK | SIRT1
NF-κB | MAPK/ERK | Wnt/β-catenin | HIF-1α

Gene regulation
Epigenetic modulation

NEUROINFLAMMATION

- Inhibit microglial activation
- Reduce pro-inflammatory cytokines (TNF-α, IL-1β, IL-6)
- Promote M2 (anti-inflammatory) phenotype
- Maintain BBB integrity

Immune Balance

M1 Microglia (Pro-inflammatory)
Shift
M2 Microglia (Anti-inflammatory)

GUT MICROBIOTA AXIS

- Modulate microbiota composition
- Increase beneficial SCFAs producers
- Enhance gut barrier function
- Reduce LPS and systemic inflammation
- Increase endogenous H_2S production

Gut–Brain Communication

- ↔ Bidirectional interaction
- → Activation / Enhancement
- ⊣ Inhibition / Suppression
- ● H_2S-mediated effect

COMMON OUTCOMES

Reduced Oxidative & Nitrosative Stress
Mitochondrial Protection
Lower Neuroinflammation
Protein Quality Control
Synaptic Preservation
Neuronal Survival & Function
Cognitive Health & Longevity

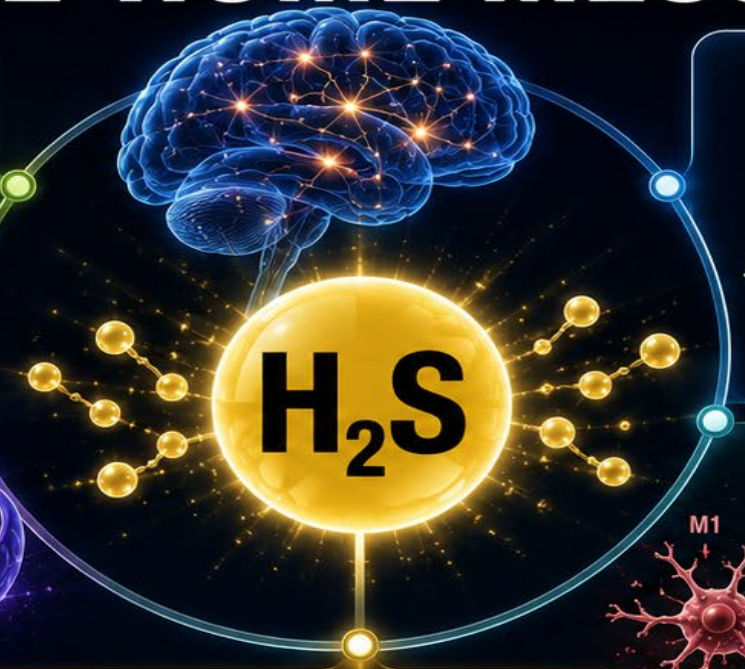
HEALTHY AGING & BETTER OUTCOMES

System biology perspective: H_2S interacts with redox homeostasis, mitochondrial function, neuroinflammation, proteostasis, epigenetics, and the gut microbiota. These interactions are bidirectional and highly interconnected. H_2S therefore acts not as a single target, but as a network regulator.

KEY TAKE-HOME MESSAGES

1 H_2S IS A FUNDAMENTAL NEUROPROTECTIVE MOLECULE.

- Endogenous signaling molecule
- Essential for cellular homeostasis
- Protects neurons against multiple stresses
- Supports brain health and function



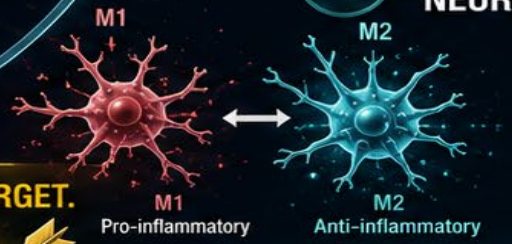
2 H_2S REGULATES REDOX HOMEOSTASIS.

- Enhances antioxidant defenses
- Scavenges reactive species
- Maintains redox balance
- Reduces oxidative and nitrosative stress

3 H_2S PRESERVES MITOCHONDRIAL FUNCTION.

- Supports ATP production
- Maintains mitochondrial dynamics
- Prevents mitochondrial damage
- Reduces apoptosis

4 H_2S MODULATES NEUROINFLAMMATION.



- Inhibits microglial overactivation
- Reduces pro-inflammatory cytokines
- Promotes M2 (anti-inflammatory) phenotype
- Protects the blood–brain barrier

5 H_2S IS A PROMISING THERAPEUTIC TARGET.

- Multi-target actions
- Broad neuroprotection
- Potential for many neurodegenerative diseases
- Basis for novel H_2S–based therapies

PROTECT NEURONS | RESTORE ENERGY | BALANCE REDOX | CALM INFLAMMATION | IMPROVE OUTCOMES

H_2S: SMALL MOLECULE, BIG IMPACT ON **BRAIN HEALTH**

H_2S is a fundamental signaling molecule with important neuroprotective functions. It contributes to redox balance, mitochondrial resilience, inflammatory regulation, and cellular homeostasis. Most importantly, H_2S biology teaches us that neuroprotection depends on maintaining balance rather than maximizing intervention."

Thank You!

HYDROGEN SULFIDE:
FROM MOLECULE TO NEUROPROTECTION

REDOX BALANCE • MITOCHONDRIAL HEALTH • NEUROINFLAMMATION
PROTEOSTASIS • MICROBIOTA

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Small Molecule. Big Impact.

BETTER BRAIN HEALTH. BETTER LIFE.