

Advanced Glycation End Products and Hydrogen Sulfide in Alzheimer's Disease: Molecular Mechanisms and Emerging Therapeutic Targets

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, amyloid- β (A β) plaque deposition, and neurofibrillary tangle formation. Emerging evidence highlights the pivotal role of advanced glycation end products (AGEs) and their receptor (RAGE) in AD pathogenesis. AGEs accumulate during aging, diabetes, and metabolic disorders through nonenzymatic glycation and glycooxidation under oxidative stress. Their interaction with RAGE activates the NF- κ B signaling pathway, promoting oxidative stress, mitochondrial dysfunction, blood-brain barrier (BBB) disruption, and chronic neuroinflammation. This AGE-RAGE axis enhances the production of pro-inflammatory mediators, including TNF- α , IL-6, MCP-1, VCAM-1, and reactive oxygen and nitrogen species (ROS/RNS), while accelerating amyloid- β aggregation, tau hyperphosphorylation, impaired mitophagy, mitochondrial dysfunction, cerebrovascular injury, and reduced A β clearance, ultimately contributing to neuronal degeneration. Hydrogen sulfide (H₂S), an endogenous gaseous signaling molecule synthesized by cystathionine β -synthase (CBS), cystathionine γ -lyase (CSE), and 3-mercaptopyruvate sulfurtransferase (3-MST), has emerged as a promising neuroprotective agent in AD. H₂S activates the Nrf2 antioxidant pathway, enhances glutathione synthesis, reduces oxidative stress, preserves mitochondrial integrity, supports long-term potentiation, modulates neurotransmission, attenuates A β -induced neurotoxicity, and suppresses neuroinflammation. Reduced H₂S levels are closely associated with cognitive impairment in AD. Overall, the AGE-RAGE axis plays a central role in AD progression, whereas H₂S acts as a protective modulator by targeting multiple pathogenic mechanisms. Therapeutic strategies that inhibit AGE-RAGE signaling while enhancing endogenous H₂S production may offer a promising approach to slowing Alzheimer's disease progression.

Keywords: Alzheimer's Disease, Advanced Glycation End Products, Hydrogen Sulfide, NF-KB pathway, Blood Brain Barrier, Mitochondrial dysfunction.

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Introduction

Alzheimer's disease (AD), the most prevalent form of dementia, progressively erodes memory and cognitive independence over time. [1, 2]. Today, approximately 44 million people globally are living with the disease, and this number is expected to increase threefold and reach about 135 million by 2050. More than half of these cases are expected to be linked to Alzheimer's disease, which demonstrates how widespread this condition is among those affected by dementia[3]. . Even after more than 100 years of research, scientists still do not know what causes Alzheimer's disease. This has led to speculation and many theories on what actually causes the condition [4]. One of the difficulties is that the symptoms patients experience don't always match up with what shows in their brains. For example, some older people have brain plaques but do not experience memory loss or other cognitive problems[5]. Additionally, many Alzheimer's patients experience neuropsychiatric symptoms alongside memory loss, which significantly impacts their daily lives and well-being. In the early stages, patients may experience anxiety, depression, and apathy. In the later stages of the illness, delusions, hallucinations, aggression, and mood swings are frequent [6, 7]. Because most patients have comorbid brain pathologies, researchers also use the term Alzheimer's disease and related dementias (ADRD) to emphasize the complex origins of cognitive loss [8]. AD has two major subtypes: the rare early-onset variant (under 5% of cases) and the prevalent late-onset variety. Although PD and AD are distinct diseases, both have complex, intertwined origins that promote disease progression in the brain [9]. Among the best-studied mechanisms is oxidative stress (OS). Butterfield and colleagues showed that long-standing redox imbalance doesn't just drive the progression of Alzheimer's disease—it also connects directly to its classic features, amyloid- β plaques, and neurofibrillary tangles[10]. This continued uncertainty about what truly triggers AD highlights the pressing need to explore fresh approaches for its prevention and treatment [11].

Redox and Glycation Stress

Oxidative stress develops when the brain produces more reactive oxygen and nitrogen species than it can neutralize. Much of this imbalance stems from faulty mitochondria, the cell's powerhouses, and the result is widespread damage to vital molecules—lipids, proteins, sugars, and even DNA and RNA[12]. Brains already vulnerable due to aging are especially prone to this stress, leaving them primed for Alzheimer's disease. In fact, even individuals with mild cognitive impairment show telltale signs: excess oxidants, weakened antioxidant defenses, and molecular damage stretching across multiple brain regions and into the body's periphery[13]. Adding further strain to the disease process is glycation stress. When sugars attach themselves to proteins, fats, or nucleic acids, they generate harmful byproducts known as Advanced Glycation End Products (AGEs). These compounds are anything but harmless—they act like molecular wrecking balls. AGEs distort normal structures, ignite inflammation, intensify oxidative stress, and accelerate the buildup of amyloid plaques and tau tangles through the AGE-RAGE signalling pathway [14, 15].

AGEs and H₂S: Opposing Regulators of Neuronal Fate

A single culprit does not drive Alzheimer's – it's a molecular tug-of-war. On one side stand AGEs, sugar-modified molecules that sabotage neurons. When advanced glycation end products (AGEs) attach to RAGE receptors, they set off a chain reaction—switching on genes that fuel inflammation and generating oxidative stress, ultimately driving neurons toward injury and death [16, 17]. On the other hand, hydrogen sulfide (H₂S) has emerged as a surprising ally, working to counteract these damaging processes. Once dismissed as just a toxic, foul-smelling gas, it is now understood to be an important signaling molecule with strong neuroprotective effects. It neutralizes reactive oxygen species, dampens inflammatory signalling, and preserves mitochondrial health, helping neurons cope with ongoing stress [18]. In this way, AGEs and H₂S stand on opposite sides – while AGEs accelerate neurodegeneration, H₂S works to defend the brain. The fate of neurons may depend on which force dominates this hidden molecular battlefield.

Pathogenic Role of AGES in Alzheimer's Disease:

The onset and aggravation of several diseases, including diabetes, atherosclerosis, AD, and the secondary ranges of Traumatic brain injury (TBI), are inspired using advanced glycation end products (AGES), which can be formed by using the nonenzymatic retort of reducing sugars with the side-chain amino companies/chain of lysine or arginine of proteins, convoyed by additional glycoxidation reactions beneath oxidative stress circumstances.[19] AGEs are labelled as: glucose is the source of AGE-1, glyceraldehydes are the source of AGE-2, Alpha Di carbonyls are the source of AGE-3, methylglyoxal is the source of AGE-4, glyoxal is the source of AGE-5, AGE-6 are composed of three-deoxyglucosone.[15] The number one scientific indication of Alzheimer's disease, a neurodegenerative disease, is growing memory and cognitive impairment. In Alzheimer's disease, the brain is marked by two classic lesions – neurofibrillary tangles (NFTs), formed from hyperphosphorylated tau, and senile plaques (SPs), made up of amyloid- β deposits. Research has shown that diabetes mellitus (DM) is a significant risk factor that increases the likelihood of AD progression.[20] People suffering from diabetes mellitus are drastically more likely to develop neurodegenerative diseases, frequently Alzheimer's disease/sickness (AD), which is characterized by amyloid plaques and neurofibrillary tangles (NFTs), Neuroinflammation, and progressive neuronal loss within the mind purpose sluggish cognitive decline and memory impairment.[21]

Activation of the NF- κ B Pathway and the Escalation of Neuroinflammatory Signalling Cascades:

In keeping with the findings, the pathophysiology of Alzheimer's might also contain Advanced glycation end products (AGES) and its receptor, RAGE (receptor for AGE). The pathophysiology of ailments has been connected to AGE-RAGE pressure, that is characterized as a stability among stressors (AGE, RAGE) and anti-stressors (sRAGE, AGE degraders) in desire of stressors.[22] Our bodies need the receptor of advance Glycation End products (RAGE) and Advance Glycation end products (AGE) to expand functions, and neurodegenerative and memory impairment illnesses are connected to their inhibition.[23] Many human problems, inclusive of diabetes, obesity, cardiovascular ailment, getting older, and so on, have lengthy been concept to be caused by the AGE-RAGE axis. Latest research has proven that the AGE-RAGE axis is worried in many pathological consequences linked to the onset of neurodegeneration, including disruption of the blood-brain-barrier, neuroinflammation, extracellular matrix remodelling, dysregulation of the polyol pathway, and antioxidant enzyme dysregulation.[24] It became cautioned that the advent of Senile Plaque inside the AD brain is as a result of both an extra aggregation of A β or a failure to dispose of and deposit A β into the brain.[25] Consistent with latest research, RAGE interacts with an extensive range of pro-inflammatory or regulatory molecules, which includes transthyretin, amyloid beta-peptide, advanced glycation end products (AGES), nucleic acids, and lysophosphatidic acid and plays a vast

function in oxidative pressure, inflammation, and cellular disorder in an expansion of ailments and conditions.[26] With getting older and metabolic failure, AGES building up within the brain, causing aberrant glucose metabolism, mitochondrial disorder, multiplied oxidative strain, and neuronal dying.[15, 27] By glycation proteins, which increases their propensity to mixture and turn out to be toxic, AGES inspire the improvement of amyloid plaque and tau pathology.[15, 28] AGES activates pro-inflammatory and oxidative pathways related to the development of AD with the aid of sending signals through the receptor for advanced glycation end products (RAGE).[29] As a likely decoy to save you dangerous consequences, the soluble version of RAGE (sRAGE) can bind a long time without triggering signalling. RAGE inhibitors and anti-glycation drug treatments are examples of therapeutic techniques that focus on AGES-RAGE signalling.[15] A complex signalling cascade is initiated when RAGE is activated, which incorporates the generation of reactive oxygen species (ROS) via the activation of NADPH oxidase, the activation of several kinases that prompt NF- κ B, STAT-3, and different proteins.[30] This ultimately lead to the synthesis of proinflammatory chemical compounds that causes infection, apoptosis, and proliferation, inclusive of as cytokines and chemokines. AGES upregulate several of these molecules, including tissue factor (TF), MCP-1, TNF- α , IL-1 β , IL-6, and VCAM-1.[31] Tumour necrosis factor-alpha (TNF- α), Interleukin-6 (IL-6), Monocyte chemoattractant protein-1 (MCP-1), and the adhesion molecules vascular cell adhesion molecule-1 (VCAM-1) and Intercellular adhesion molecule-1 (ICAM-1) are some of the predominant inflammatory mediators which might be precipitated. These mediators influence the recruitment of immune cells and vascular inflammation inside the brain.[32] Complex intracellular signalling cascades that disrupt cellular homeostasis and brain physiological features are induced by using the interaction of advanced glycation end products (AGES) with the receptor for advanced glycation end products (RAGE) on the cell surface. [33] Crucially, through increasing the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which accentuate NF- κ B signalling, NF- κ B activation additionally creates a self-reinforcing comments loop.[34] The slow and irreversible route of Alzheimer's disorder is as a result of diseased surroundings created with the aid of the AGE-RAGE axis's vicious cycle of irritation and oxidative stress.[34]

Link between Mitochondrial Dysfunction and AGES:

By interacting with their receptor RAGE on neurons and glia, AGES cause signalling that impairs mitochondrial function and increases oxidative pressure. Neuronal injury and dying are promoted by using this interaction, which leads to abnormalities of the mitochondria, together with reduced electron transport chain (and so on) activity, increased formation of reactive oxygen species (ROS), and modified mitochondrial dynamics. [35] AGES leads to mitochondrial harm by way of encouraging tau hyperphosphorylation and amyloid beta aggregation.[36] Amyloid beta exacerbates mitochondrial dysfunction by using directly interacting with mitochondrial proteins. This connection creates a comments loop wherein advert pathogenesis is multiplied by way of mitochondrial harm.[37] Because of AGE-RAGE signalling interference with mitochondrial fission-fusion stability and mitophagy (the removal of damaged mitochondria), defective mitochondria acquire, which raises ROS and mobile stress. [38, 39]

Interaction Between AGES and A β Aggregation Pathways:

By means of converting the peptide and its aggregation pathway, Advance glycation end products (AGES) play a first-rate function in the aggregation of amyloid beta (A β) in Alzheimer's disease (AD).[40] A β is one of the proteins and peptides which might be nonenzymatically glycated to create AGES. This method encourages the advent of everlasting cross-hyperlinks that enhance A β fibrillization and plaque

improvement.[41] This glycation quickens the deposition of amyloid plaque inside the brain by means of prolonging the half of-life of A β and growing its accumulation by reducing degradation.[15] Glycation alters the structure of A β , causing conformational changes that promote the development of β -sheets, an crucial stage in the meeting of amyloid fibrils.[42] Amyloid aggregates become greater toxic and stable as a result of these modifications. Furthermore, by using disrupting clearance strategies like autophagy, AGES increases amyloid accumulation by way of encouraging protein misfolding and aggregation. Improved AGE production and next A β glycation are made worse with the aid of extended glucose or carbonyl metabolites, which connects advert hazard to metabolic dysfunction (such as diabetes).[40] Moreover, AGE-changed A β interacts extra potently with receptors which includes RAGE,[43] resulting in elevated inflammation and oxidative strain, which in addition inspire amyloidogenic techniques and neuronal damage.[33] This exaggerates AD pathophysiology by means of producing a malicious cycle of oxidative harm, AGE-A β collaboration, and aggregation.[25]

Vascular and Blood-Brain Barrier Dysfunction Instigated by AGE in the Expansion of Alzheimer's Disease:

A precursor to Alzheimer's ailment, vascular dysfunction takes place when the blood-brain-barrier (BBB) is dented via AGE, allowing toxic elements like amyloid- β to reach the brain and instigating tau and amyloid stockpile. AGE-RAGE interactions cause inflammation and oxidative strain, which compromises the integrity of the blood-brain barrier, lowers cerebral blood flow, and hinders the elimination of A β , all of which hasten neurodegeneration.[44] Studies screen a connection between extended AD danger and vascular hazard elements such as metabolic syndrome, diabetes, and high blood pressure, diseases related to increased AGE development.[45] Increased BBB permeability, compromised cerebral blood flow, and vascular endothelial disorder are all results of those hazard factors.[46] Furthermore, by changing tight junction proteins and compromising the activity of endothelial cells that manage brain homeostasis, AGES compromise BBB safety.[47] Neurodegeneration arises from BBB endothelial cellular dysfunction that limits toxin clearance and nutrient shipping, with APOE4-associated vascular vulnerability worsening AGE-prompted BBB breakdown and amplifying oxidative strain and amyloid pathology.[41]

Protective role of Hydrogen Sulfide in Alzheimer's disease:

Hydrogen sulfide has turn out to be a key endogenous gaseous signaling molecule in neuroscience,[48] having crucial protective functions in the brain, specifically in Alzheimer's disease.[49] One extensive endogenous chemical with neuroprotective capability in Alzheimer's disease is hydrogen sulfide (H₂S).[50] It is often synthesized in the mind by using 3-mercaptopyruvatesulfurtransferase (3-MST), cystathionine β -synthase (CBS), and cystathionine γ -lyase (CSE). Whereas CSE predominates in neurons, CBS is generic in astrocytes. Decrease H₂S stages and reduced neuroprotection are resulting from decreased expression and activity of CBS and CSE mainly in AD. [51, 52] The Nrf2 pathway is in the main activated through endogenous H₂S to offer protective benefits in Alzheimer's disease.

Nrf2 pathway activation

H₂S acts as the brain's built-in shield, mainly by activating the Nrf2 defense pathway[53]. Through persulfidation of Keap1, H₂S stabilizes Nrf2 and drives its entry into the nucleus, where it switches on antioxidant genes such as HO-1 and GCLC, boosting glutathione production and easing oxidative stress[54-56].At the same time, Nrf2 enhances SOCS3 expression, which silences pro-inflammatory cytokines, reducing microglial hyperactivity and calming chronic neuroinflammation[57]. Collectively, these dual antioxidant and anti-inflammatory actions cut down ROS overload, block A β buildup, prevent

tau hyperphosphorylation, and safeguard mitochondria—ultimately protecting neurons, preserving cognition, and countering the AGE–RAGE driven damage seen in Alzheimer’s disease brains. [41, 58, 59].

SIRT3 Activation

H₂S sparks up sirtuin activity with SIRT3, the powerhouse protector, taking center stage. By fueling metabolism, fighting oxidative stress, and calming inflammation, SIRT3 activation is rising as a bold new shield against Alzheimer’s disease [60]. H₂S supercharges sirtuins like SIRT3 through smart tweaks such as sulfhydrylation flipping on pathways that cut down oxidative stress, cool inflammation, and fuel brain cell longevity[60]. SIRT3 is the mitochondria’s bodyguard when it’s missing, the brain faces more inflammation, amyloid buildup, and a leaky blood–brain barrier, all fueling Alzheimer’s damage[61, 62].

Experimental Evidence

Boosting H₂S (like with NaHS) in AD models cools inflammation, cuts oxidative stress, and improves brain structure. While miRNAs play a role, SIRT3 stands at the core, guarding mitochondria and blocking neurodegenerative cascades. [60, 63]. A healthy gut and steady H₂S levels team up to boost SIRT3, unlocking a powerful synergy that may shield the brain and slow Alzheimer’s and other neurodegenerative diseases[64].

Neuroprotective Implications

Activating SIRT3 with various compounds sharpens cognition, powers up mitochondrial cleanup, and cuts down amyloid build-up in Alzheimer’s models[65]. SIRT3 fine-tunes key enzymes like IDE and neprilysin that clear amyloid-beta. Boosting it with H₂S or other activators could strike directly at the heart of Alzheimer’s pathology[66].

Interplay and Imbalance: The Tug-of-War Hypothesis

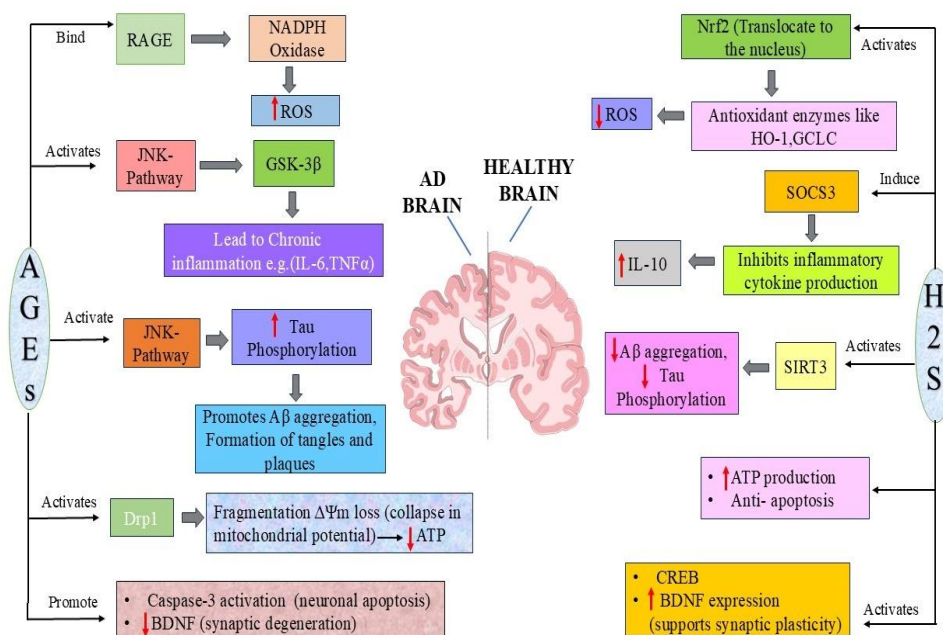


Figure 1: In Alzheimer's, AGEs fuel stress, inflammation, and amyloid buildup but H₂S fights back, switching on SIRT3 and antioxidant shields to keep mitochondria and neurons protected.

Table 1: AGES inhibitor pharmacological profile

Compounds Name	Primary Mechanism of action	Key Therapeutic Indication	Key clinical findings	Pre- clinical and clinical status
Amino-guanidine	-Prevents advanced glycation end products (AGEs) from forming, by reacting quickly with α , β -Dicarbonyl molecules such methylglyoxal, glyoxal, and 3-deoxyglucosone	-Diabetic Retinopathy, Diabetic Nephropathy, General Diabetic Complications	-Prevents AGE accumulation besides pathological features in investigational diabetic retinopathy. No beneficial effects on development of overt nephropathy in human trials	-Clinical Trials (ACTION-1, ACTION-2) finalized. -Action-1 study on patients with Type-1 diabetes and Action-2 study on patients with Type-2 diabetes
Pyridoxamine	- As a post-Amadori inhibitor, pyridoxamine suppresses the production of AGE and advanced lipoxidation end products and lowers hyperlipidaemia	-hyperlipidaemia, Diabetic neuropathy	-prevents shortfalls in recognition memory, Confirmed pharmacological latent for diabetic neuropathy and hyperlipidaemia	- pre-clinical trials of cognitive dysfunction in diabetic rats
Alagebrium (ALT-711)	-breaks reputable AGE cross-links between proteins.	-Cardiovascular diseases, hypertension, diastolic heart failure	-Condensed large artery stiffness and enhanced cardiac function in animal models. - Alagebrium did not change blood pressure, VO ₂ , or aortic distensibility, but it did decrease left ventricular mass and correct diastolic function as observed in Clinical trial phase 2.	-Preclinical studies-Studies using ALT-711 in animal models (confirmed its ability to reverse diabetes and cardiovascular problems associated with aging). -Clinical studies-Phase 1, Phase 2, Phase 3, completed and Phase 4 clinical studies are terminated in 2009, In 2013 again it was terminated.

Table 2: Hydrogen Sulfide Donors

Compound Name	Primary mechanism of action	Key Therapeutic Indications	Key Clinical Findings	Pre-Clinical/ Clinical Status	References
GY4137	slow-releasing hydrogen donor that breaks down on its own in aqueous buffers to maintain low levels of hydrogen sulfide	-Cardiovascular diseases (vasodilator, antihypertensive, cardioprotective)	-Vasodilator and antihypertensive, protective against cardiac dysfunction in type-2 diabetes mellitus in rats	Primarily studied in preclinical <i>in vivo</i> and <i>in vitro</i> models. No active clinical trials in 2024-2025	[70]
ACS84	Hybrid molecule releasing both dopamine (from L-DOPA moiety) and hydrogen sulfide. Act as antioxidant, anti-inflammatory, mitochondrial protectant, and neuroprotectant	-Parkinsons Disease, Neurodegenerative diseases	-Improved motor defects, reduced neuronal loss and elevated dopamine in Parkinsons disease rat models. DOPA and NaHS alone protecting against cell injury.	- Primarily studied in preclinical <i>in vitro</i> and <i>in vivo</i> models. -No active trials in 2024-2025	[71]

Conclusion

Alzheimer's disease is a complicated neurodegenerative disease that involves multiple areas of pathology (e.g. oxidative stress, lot of protein glycation and chronic inflammation). The driving force behind this pathological process, and the causative factor for neurodegeneration, is the AGE-RAGE signaling axis, which facilitates amyloid- β accumulation, tau hyperphosphorylation, mitochondrial dysfunction, neuroinflammation, and the disruption of the blood-brain barrier. All this further contributes to accelerating neurodegeneration and subsequent neuron loss. In contrast, H_2S , a gas generated naturally in the brain, is a potent protector of against these pathological processes. H_2S -defends the mitochondria, decreases oxidative stress, reduces inflammation, and preserves synaptic plasticity. H_2S -induced bolstering of antioxidant defenses- such as glutathione-and stabilization of cellular energy homeostasis through Nrf2 and SIRT3 pathways, confronts toxic consequences in part due to amyloid and tau. There are now many animal and *in vitro* studies in which H_2S not only restores mitochondrial homeostasis, but also enhances memory and cognitive performance. Thus, a novel therapeutic approach is emerging: Alzheimer's can be effectively treated on both sides of the toxicity challenge, i.e. by inhibiting the pathological AGE-RAGE axis, while at the same time emphasizing H_2S -mediated defense processes in the brain. In the future, anti-glycation compounds, RAGE inhibitors, H_2S donors, could lead the way in practice to the development of

new drugs that could treat Alzheimer's disease by slowing or stopping its progression, and thus preserving the brain's resilience.

Author contribution

SS: Data collection, drafting the original version, PS: Arranged the table, GC: Arranged the figures.

Data Availability

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