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Carbon Dioxide–Calcium Crosstalk in Alzheimer's Disease: A Mechanistic Model of Neurodegeneration

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ABSTRACT

Background: The incidence of Alzheimer's disease has risen in parallel with increasing atmospheric carbon dioxide (CO_2) levels over the past century.

Objective: To investigate whether elevated CO_2 levels are associated with Alzheimer's disease. **Design:** A case-control study conducted at tertiary hospitals in Egypt.

Methods: A total of 78 patients diagnosed with Alzheimer's disease and 45 age- and sex-matched controls (65–76 years old) were enrolled. All participants underwent clinical examination and completed a standardized questionnaire collecting demographic information, including age, sex, occupation, smoking status, family history, and history of chronic respiratory disease or occupational CO_2 exposure, in accordance with the National Institute for Occupational Safety and Health criteria (August 1976). Recruitment occurred between November 2023 and October 2024. Arterial blood gas analysis was performed for all participants, and selected patients underwent additional evaluations to confirm the diagnosis of Alzheimer's disease, where applicable. $PaCO_2$ levels were analyzed using two independent statistical methods to assess significance. **Results:** The mean $PaCO_2$ (± SD) was 46.20 ± 2.26 mmHg in patients with Alzheimer's disease compared to 43.73 ± 3.02 mmHg in controls, with a standard error (SE) of 0.518 and a 95% confidence interval of 1.44–3.50 ($P < 0.0001$). Elevated $PaCO_2$ was observed in 54 (69.2%) cases and 9 (20.0%) controls ($P < 0.00001$). **Conclusion:** This study demonstrates a significant association between elevated CO_2 levels and Alzheimer's disease. The underlying mechanisms may involve CO_2-induced alterations in cell membrane integrity, calcium

homeostasis, and intracellular signaling pathways. CO_2-related acidification may impair β-amyloid–clearing enzymes by disrupting zinc-binding histidine residues, thereby promoting Aβ accumulation, while its thermogenic effect may accelerate microtubule degradation and neuronal instability. These findings highlight CO_2-associated pathways as potential therapeutic targets, including strategies to limit CO_2 accumulation or diffusion and the use of hyperbaric oxygen therapy to mitigate CO_2-driven receptor modulation and neuroinflammation.

.**Keywords**: CO_2; Ca^{2+}; Alzheimer's disease; Amyloid; Calcium

INTRODUCTION

The incidence of neurodegenerative disorders has markedly increased over recent decades. Neurological disorders are now the leading cause of physical and cognitive disability worldwide, affecting approximately 15% of the global population. The absolute number of patients has risen substantially over the past 30 years [1]. This trend parallels the escalating risks associated with carbon dioxide (CO_2) emissions and climate change recognized as significant threats to humanity's future [2]. While the environmental impacts of CO_2 have been widely discussed and studied—particularly their economic consequences—their effects on human health have received far less attention and remain insufficiently investigated. This work aims to alert the scientific community by presenting evidence that elucidates the health risks of CO_2 exposure, thereby opening a largely underexplored research field.

Future CO_2-related research should focus on elucidating the underlying pathophysiology, developing strategies for disease prevention, modification, and treatment, and identifying novel biomarkers to enable early diagnosis, detect subclinical disease progression, and monitor therapeutic responses. Enhancing dementia screening, detection, and diagnosis remains a key priority of this mission.

Epidemiology. Alzheimer's disease (AD) is the most common cause of dementia in older adults (≥65 years) and represents a major global health challenge. The worldwide burden of AD is evident from rising prevalence, incidence, and mortality rates. Mild cognitive impairment (MCI) due to AD often progresses to dementia, with estimates of AD-related dementia among MCI patients ranging from 40% to 75%, depending on the population studied and the diagnostic criteria used [3]. AD accounts for approximately 60–80% of dementia cases globally. Age is the strongest risk factor: early-onset AD (<65 years) is rare and represents <5% of cases, while prevalence roughly doubles every five years beyond age 65. Women face a higher risk, partly due to their longer life expectancy and potentially due to biological factors.

***Global Statistics*.** As of 2023, an estimated 55 million people live with dementia, of whom 60–80% have AD. This number is projected to reach approximately 139 million by 2050 [4–6].

Pathology of Alzheimer's Disease. Neurodegenerative diseases share common pathological and clinical features, including selective vulnerability of specific brain regions and aggregation of misfolded proteins [7]. In AD, pathology is characterized by extracellular amyloid plaques and intracellular neurofibrillary tangles (NFTs), often surrounded by activated immune cells, particularly microglia. Clinically, AD manifests as progressive cognitive decline [8]. The principal component of amyloid plaques is amyloid beta (Aβ), generated by abnormal cleavage of amyloid precursor protein (APP). NFTs consist of hyperphosphorylated tau, a microtubule-associated protein. While Aβ and tau accumulation are central to AD pathology, the precise mechanisms driving their formation remain incompletely understood [9]. Aβ deposition begins in the preclinical

phase, and individuals may harbor Aβ plaques for more than a decade before symptom onset [10]. Tau pathology generally develops downstream of Aβ accumulation [9]. Deposited Aβ is thought to act as a damage-associated molecular pattern (DAMP), engaging receptors such as toll-like receptors (TLRs), the receptor for advanced glycation end products (RAGE), and nucleotide-binding oligomerization domain-like receptors (NLRs). This interaction activates microglia, triggering the release of cytokines and chemokines and recruiting additional glial cells to the site of Aβ deposition [11].

Microglia and astrocytes can phagocytose Aβ via multiple receptors to protect neurons [12]. However, inefficient clearance leads to chronic inflammation and the release of pro-inflammatory and neurotoxic mediators, including cytokines, chemokines, reactive oxygen species (ROS), and nitric oxide (NO), which exacerbate neuronal damage [10,13]. Other central nervous system (CNS) cell types, such as neurons, oligodendrocytes, vascular endothelial cells, and pericytes, also contribute to sustaining this inflammatory microenvironment [14,15]. Activated microglia may further promote Aβ plaque formation by increasing Aβ fragment secretion, inducing interferon-induced transmembrane protein 3 (IFITM3, a γ-secretase modulatory protein), or releasing metals such as copper that enhance Aβ aggregation [15–17]. Because microglial activation precedes tau aggregation and promotes tau hyperphosphorylation, it ultimately drives NFT formation [18]. Accumulated tau tangles disrupt neuronal function, trigger apoptosis, and promote immune cell activation [19] (Figure 1).

NFTs are also spatially associated with neuroinflammation in human AD brain samples [20,21]. Meng et al. demonstrated that hyperphosphorylated tau can disrupt membrane bilayers and activate human macrophages via TLR4 [22]. More recently, Welikovitch et al. reported that neurons laden with soluble and oligomeric Aβ display a distinctive inflammatory signature. This neuron-specific inflammatory response may precede the formation of insoluble Aβ plaques and tau tangles, suggesting that intraneuronal Aβ accumulation is an early pathological event with a substantial immunological component [23].

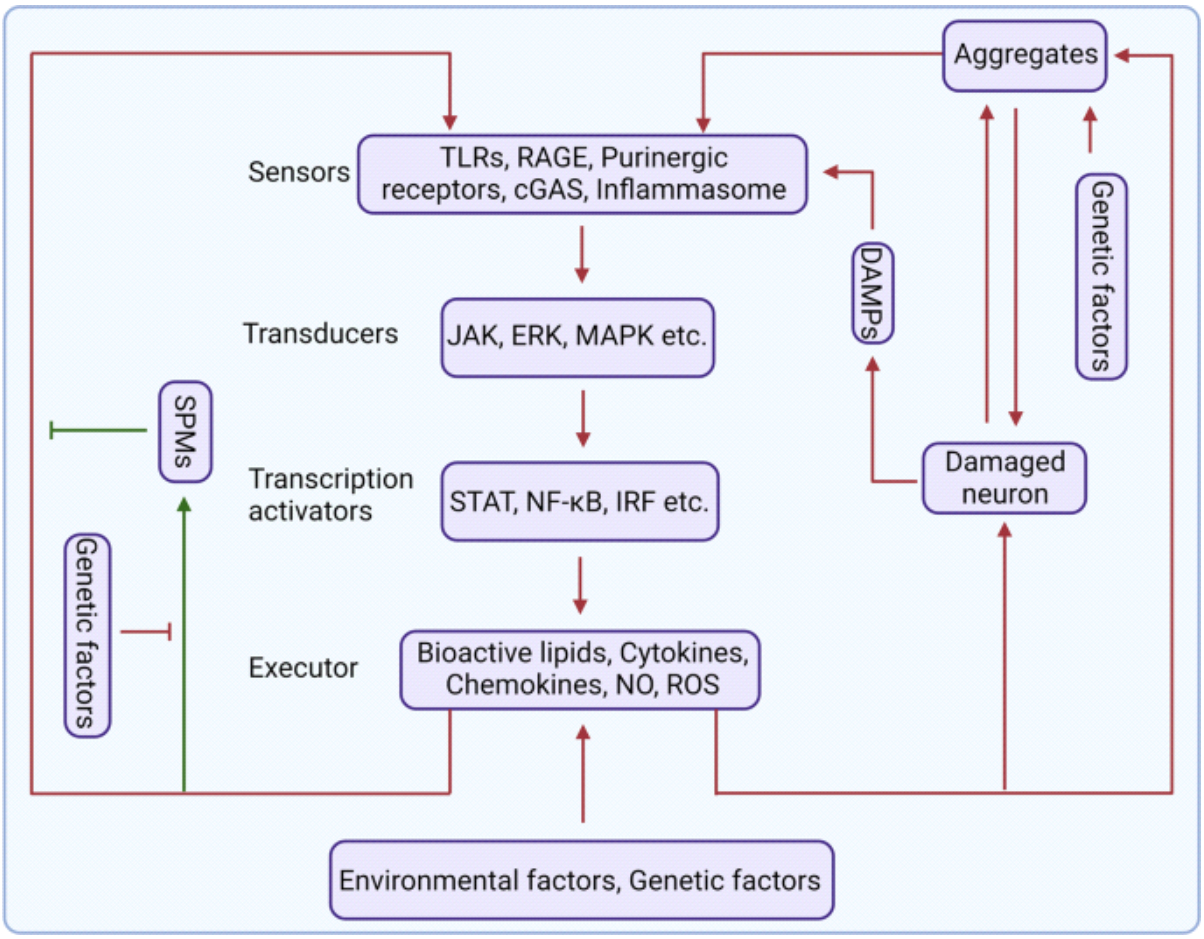

Figure 1: Integrated Model of Inflammatory Signaling in Neurodegeneration

Inflammatory receptors on the surface of immune cells, particularly glial cells, act as sensors that detect abnormalities in the human body. Stimulation of these receptors by damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs)—such as protein aggregates, viruses, or bacteria—activates intracellular signal transducers, which in turn stimulate transcription factors. These transcription factors promote the secretion of inflammatory mediators, thereby amplifying the inflammatory response [10].

The Relationship Between Carbon Dioxide (CO_2) and Alzheimer's Disease (AD). This is an emerging research area, especially considering recent findings related to cerebral blood flow, neuroinflammation, and acid–base imbalance.

1. CO_2, Cerebral Blood Flow, and Hypoxia. Elevated arterial CO_2 (hypercapnia) causes cerebral vasodilation. However, chronic CO_2 elevation can impair cerebral autoregulation and oxygen delivery. Hypercapnia also alters blood–brain barrier (BBB) permeability and may exacerbate hypoxia-induced neuronal injury. Impaired cerebral perfusion contributes to vascular dementia and increases the risk of AD [24,25].

2. CO_2 and Brain pH (Acidosis). CO_2 reacts with water to form carbonic acid, lowering brain pH. Acidosis affects:

- Enzyme function, increasing amyloid β-protein (Aβ) expression in hippocampal neurons and promoting Aβ accumulation [24].
- Tau phosphorylation and aggregation [25].

3. CO_2 and Neuroinflammation. Elevated CO_2 has been linked to activation of inflammatory signaling, including interleukin-1β production. The NF-κB and NLRP3 inflammasome pathways are activated under hypercapnic conditions [26–28]. While microglia play a protective role in clearing Aβ plaques during the early stages of AD, their chronic activation can have detrimental consequences, such as exacerbating tau pathology and promoting neuronal apoptosis [29].

4. CO_2, Protein Aggregation, and Clearance. CO_2-induced acidosis impairs protein clearance mechanisms. Alterations in endosomal and lysosomal pH, along with global brain acidification, are associated with increased amyloid-β aggregation and reduced solubility [30].

5. Experimental Models Linking CO_2 to AD-like Changes. Animal studies suggest that CO_2 exposure can directly influence AD pathology. Chronic hypercapnia in rodent models has been shown to increase APP expression, promote Aβ accumulation, and enhance tau phosphorylation [31].

Summary

Carbon dioxide may contribute to Alzheimer's disease through multiple interconnected mechanisms:

- Disruption of cerebral blood flow and oxygenation.
- Brain acidosis leads to altered calcium signaling and enzyme activity.
- Activation of neuroinflammatory pathways.
- Impaired clearance and increased aggregation of amyloid-β and tau proteins.

Methods

To our knowledge, this is the first study to investigate the role of CO_2 in the pathogenesis of Alzheimer's disease. It is important to note that, due to the presence of uncontrolled extraneous variables, this study can suggest a possible association but cannot establish causality. The assessment of arterial partial pressure of CO_2 ($PaCO_2$) has long been considered a gold standard in clinical evaluation. These measurements are particularly relevant in the context of climate change and indoor air quality, as they inform ventilation standards. Furthermore, calculations involving CO_2 production and oxygen consumption yield metabolic indices that can be further explored in various fields [30]. Based on exclusion criteria designed to minimize confounding, CO_2 exposure was selected as a primary variable in both the study design and assessment.

Study Design. This case-control study employed participant selection based on established matching criteria linked to known associations with the outcome of interest.

Setting and Participants. The study was approved by the administrative boards of Hurghada, Marsa Alam, and Nasser Institute Hospitals in Cairo, Egypt. Informed consent for laboratory testing was obtained from all participants in accordance with hospital regulations. The study protocol adhered to the ethical standards of the 1975 Declaration of Helsinki.

Variables. Cases and controls were matched for potential confounders and recruited from the same geographic and demographic population. Parameters such as age, sex, urbanization level, socioeconomic status, and comorbidities were balanced between groups. Demographic data were collected via questionnaire, including

age, sex, occupation, smoking status, family history, and history of chronic respiratory illness or occupational CO_2 exposure, in accordance with the criteria set by the National Institute for Occupational Safety and Health (August 1976). Individuals working in farming, mining, or CO_2-related industries were excluded.

Data Sources and Measurement. Cases were identified from patient rosters at participating hospitals, while controls were drawn from the same source population. Both groups were matched by sociodemographic factors. Eligible cases were recruited from both outpatient and inpatient settings. Arterial blood gases were measured using the ABL90 FLEX PLUS analyzer to determine Pa CO_2 levels. Participants were stratified based on whether their $PaCO_2$ values were above or below the median. The standard reference range for $PaCO_2$ was 35–45 mmHg.

Sample Size and Bias. Between October 2024 and June 2025, 78 cases (40 males, 38 females) and 45 controls (24 males, 21 females), aged 65–76 years, were enrolled. While the group sizes differed, the primary focus was on the percentage of event occurrence and the comparative strength of association, both of which are appropriate indicators in case–control studies. The analysis was restricted to CO_2 exposure and validated using two statistical methods: percentage of event occurrence and mean ± standard deviation.

Quantitative Variables. Participants were screened to exclude conditions affecting $PaCO_2$, such as cardiopulmonary diseases, obstructive sleep apnea, critical illness, and multisystem organ failure. Diagnostic testing for Alzheimer's disease was conducted when clinically indicated.

Statistical Analysis. Data were either normally distributed or the sample size was sufficient for the Central Limit Theorem to apply. Independent group comparisons were performed using manual calculations equivalent to the following software tools: IBM SPSS v29, R (v4.3.1), and Python's SciPy module (stats.ttest_ind with equal_var=False). Demographic characteristics were compared using t-tests, adjusted odds ratios, 95% confidence intervals (CIs), and p-values.

Alzheimer's Disease Diagnostic Criteria:

- Gradual onset (over months to years).
- Progressive cognitive decline, typically beginning with memory impairment and potentially affecting language, visuospatial skills, and executive function.
- Interference with daily functioning.
- Not explained by other causes (e.g., stroke, depression, or other dementias).
- Supportive features (not required):
- Biomarkers (CSF, PET) indicating amyloid and tau pathology.
- MRI showing medial temporal lobe atrophy.

Diagnostic Categories:

A. *Probable AD dementia*: Typical presentation with functional impairment.
B. *Possible AD dementia*: Atypical presentation or mixed pathology.
C. *Mild Cognitive Impairment due to AD*: Memory decline without complete loss of independence [33–35].

RESULTS

Table 1: Demographic characteristics of cases and controls.

Variable	Cases No. (%) (n =78),	Controls No. (%) (n =45),	Odds ratio, or Mean difference (95% CI), P value
Sex (female)	33 (42.3)	20(44.4)	OR=0.92 [0.44, 1.92] p ≈ 0.82
Age, mean (S.D.), years	71.29 ±1.63	70.84 ± 2.17	MD = 0.45 [-0.28, 1.18] P ≈ 0.23
Total annual outcome, $ ≤ 12000. 12000 – 30000 ≥ 30000	 47 (60.3) 25 (32) 6 (7.7%)	 27 (60.0) 14 (31.1) 4 (8.9)	
Smokers	16 (20.5)	8 (17.8)	1.19 [0.46, 3.05], P ≈ 0.72

No statistically significant association between case/control status and smoking ($p > 0.05$). There was no statistically significant difference in age between cases and controls. Similarly, no significant difference was observed in the odds of being female between the two groups ($p > 0.05$). Additionally, smoking status was not significantly associated with case/control classification ($p > 0.05$).

Table 2: *Comparison of mean partial pressure of carbon dioxide (Pa CO_2) in arterial blood between cases and controls*

Group	N	Mean Value of $PaCO_2$	SD	SE, 95% C I	P value
Cases	78	46.20	2.26	0.518, (1.44, 3.50)	< 0.0001
Control	45	43.73	3.02		

Note: Pa CO_2 = partial pressure of carbon dioxide in arterial blood. There was a highly significant difference in Pa CO_2 between cases and controls.

Table 3: *Comparison of elevated Pa CO_2 rates between cases and controls*

Group	No. (%) with elevated $PaCO_2$	No. (%) without elevated $PaCO_2$	Total
Cases	54 (69.2)	24 (30.8)	78
Controls	9 (20.0)	36 (80.0)	45
Total	63	60	123

The *p*-value for a two-tailed test was < 0.00001, indicating an extremely significant difference in the proportion of subjects with elevated Pa CO_2 between cases and controls.

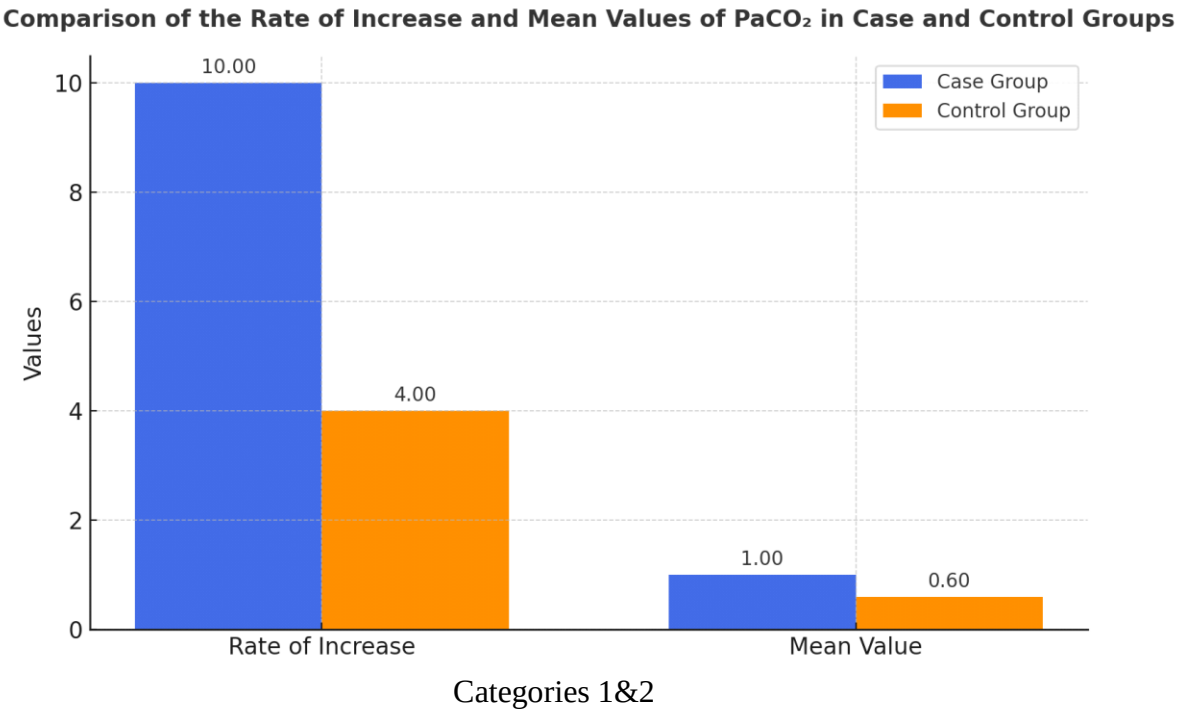

Figure 2: Blue columns represent cases. Brown columns represent controls.
Category 1: Rate of increase in Pa CO_2.
Category 2: Mean Pa CO_2 values.

DISCUSSION

The world is currently facing an unprecedented and life-altering challenge in response to climate change. The unique physicochemical properties of carbon dioxide (CO_2) significantly influence cellular electrical potential, pH regulation, thermal capacity to absorb and re-emit infrared radiation, gas-like diffusivity, and liquid-like solvating power.

This study is the first to elucidate the association between carbon dioxide (CO_2) and the increased incidence of Alzheimer's disease (AD). Our findings indicate that the partial pressure of arterial CO_2 ($PaCO_2$) is directly proportional to the number of AD cases. Although no prior research has documented this relationship, we identify multiple pathogenic mechanisms implicated in AD etiology. These appear to be mediated through downstream pathways triggered by CO_2's direct effects on Tau–microtubule functional integrity, alterations in the enzymatic clearance of β-amyloid, and CO_2-mediated disruption of calcium channels and intracellular signaling.

Given recent advances in calcium (Ca^{2+}) signaling research and the growing prevalence of neurodegenerative diseases, we explored CO_2's potential role in the pathogenesis of such disorders, primarily AD. We propose a

mechanistic model integrating CO_2, Ca^{2+} signaling, calcium channels, secondary messengers, and AD progression. This model is supported by evidence of a precise link between CO_2 and Ca^{2+} signaling. Notably, Ca^{2+} signals encode information via their frequency, kinetics, amplitude, and spatial distribution, enabling complex intra- and intercellular communication.

CO_2's multifaceted actions may contribute to neurodegeneration through interconnected pathways involving membrane receptors, cytokines, interleukins, genes, and messenger RNAs. Collectively, our results support the hypothesis that CO_2 can initiate, stabilize, and sustain AD pathogenesis. Kumar et al. recently highlighted the link between cytokine-mediated disorders and antioxidant-based therapies [36]. CO_2 possesses distinctive physicochemical traits—such as becoming a supercritical fluid above its critical temperature and pressure, exhibiting both gas-like diffusivity and liquid-like solvating power, and demonstrating high aqueous solubility—that make it a compelling research target [37]. Its capacity to absorb and re-emit infrared radiation underlies its central role in anthropogenic climate change. Given its long atmospheric lifetime and cumulative radiative forcing, CO_2 remains the primary target of global emission reduction and carbon capture strategies [38].

In aqueous environments, CO_2 forms carbonic acid (H_2CO_3), which rapidly equilibrates with bicarbonate and carbonate ions [39]. Elevated temperatures promote water autoionization and shift acid–base equilibria in accordance with Le Chatelier's principle, lowering solution pH—a phenomenon well established both theoretically and experimentally [40]. We suggest that this acidification could contribute to AD pathogenesis by altering protein conformation, enzyme activity, and neuronal microenvironments. Preliminary evidence also suggests a potential association between CO_2 and autoimmune disorders [41,42], with recent mechanistic insights provided by Abdelrazak et al. [43]. Increasing recognition of immune dysregulation in neurodegeneration—supported by the discovery of immune-related genetic risk factors—has spurred interest in targeting neuroinflammation to prevent central nervous system damage [10].

We further propose that CO_2-driven acidification may protonate histidine residues, leading to imidazole ring ionization and conformational shifts that activate heterotrimeric G proteins, increase intracellular cAMP, and modulate signaling. This pH-responsive behavior of histidine is relevant to the acidic brain environments observed in AD [44–46].

Our findings also suggest that mechanical and thermally induced membrane fluctuations can modify subcellular receptor topology, influencing cellular signaling and protein folding. CO_2 may exacerbate protein misfolding via:

- Intracellular Acidosis — destabilizing hydrogen bonds, electrostatic interactions, and disulfide bridges [48].
- Protein Carbamylation — altering protein charge and structure through non-enzymatic CO_2 reactions [49].
- Chaperone Dysfunction — impairing HSP-mediated folding under hypercapnic stress [50].
- Endoplasmic Reticulum Stress — activating the unfolded protein response, leading to apoptosis [51].

Additionally, receptor topology changes may impair immune-mediated β-amyloid clearance [52], while elevated temperatures can destabilize microtubules and collapse their networks [53–55]. Acidic conditions may also

inhibit β-amyloid–degrading enzymes—many of which are zinc-dependent metalloproteases—by protonating histidine residues critical for catalysis [45, 58–60].

In short. By comparing LRRK2 and β-amyloid–degrading enzymes, we consider: LRRK2, a leucine-rich repeat kinase, relies on conserved lysine and aspartate residues rather than histidine for catalysis and is therefore insensitive to histidine protonation. In contrast, β-amyloid–degrading enzymes—such as IDE, NEP, ECE, and MMPs—are zinc-dependent metalloproteases with histidine-rich motifs critical for Zn^{2+} coordination. Acidic conditions, including CO_2-induced acidosis, protonate these histidines, impairing Zn^{2+} binding and catalytic efficiency.

Taken together, these findings support a multifactorial model in which CO_2 contributes to AD pathogenesis through biochemical, biophysical, and immunological mechanisms.

Mechanism-Focused Summary of LRRK2 in Alzheimer's Disease

A. Neuroinflammation: LRRK2 is highly expressed in microglia and enhances the production of pro-inflammatory cytokines (e.g., TNF-α, IL-1β), thereby exacerbating neuroinflammation. It may also mediate ferroptosis via the p62–Keap1–Nrf2 signaling cascade [61, 62].

B. Tau Phosphorylation: LRRK2 kinase activity promotes abnormal tau phosphorylation, facilitating the formation of neurofibrillary tangles [63].

C. Autophagy–Lysosomal Dysfunction: LRRK2 regulates lysosomal trafficking, and its hyperactivity impairs autophagy, reducing the clearance of Aβ and tau. Inhibition of LRRK2 restores autophagy and mitigates inflammation-induced dysfunction [64].

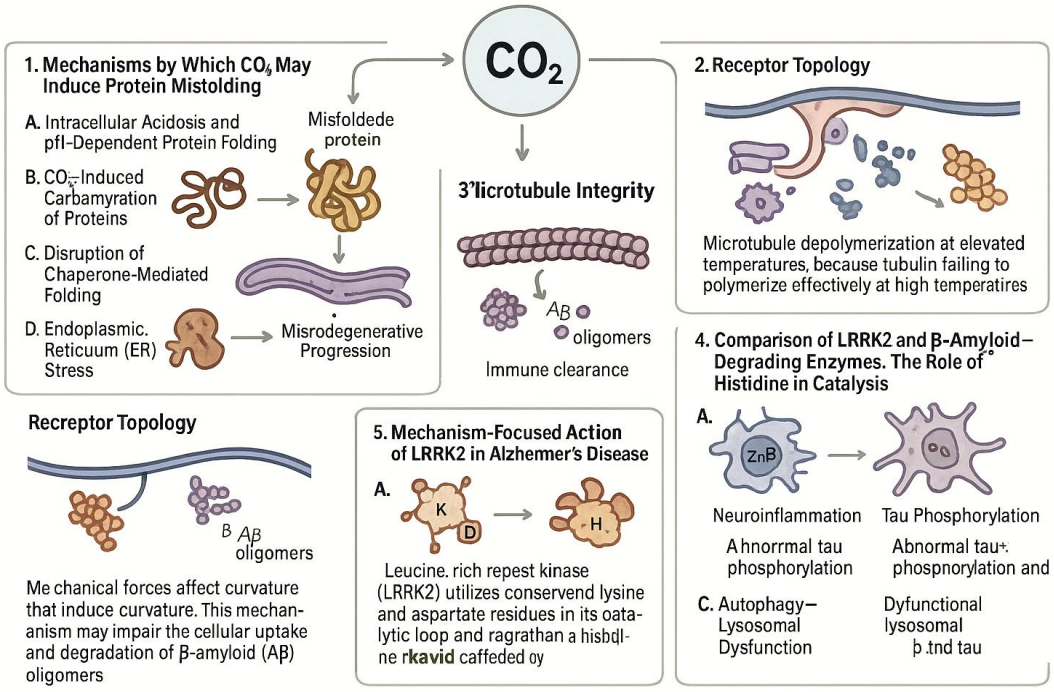

Figure 3: Mechanisms by which carbon dioxide (CO_2) may contribute to the development of Alzheimer's disease:

Functional Disruption of Ca^{2+} Signaling in Neurodegeneration and Therapeutic Implications

Intracellular Ca^{2+} homeostasis, maintained by Ca^{2+} binding proteins, voltage-gated calcium channels (VGCCs), pumps, transporters, and intracellular stores, is essential for neuronal excitability, connectivity, and survival. Dysregulation disrupts mitophagy, promotes oxidative stress, and accelerates neuronal loss—hallmarks of neurodegenerative diseases (NDs) [65,66]. Emerging miniscope imaging data indicate that calcium deficits at the neural network level may underline clinical symptoms more effectively than single-neuron models, underscoring the need for circuit-targeted therapies [67]. In Alzheimer's disease, intracellular Ca^{2+} overload is driven largely by amyloid-β (Aβ) oligomers, which form Ca^{2+} permeable pores and hyperactivate L-type calcium channels (LTCCs), NMDA receptors, and ryanodine/IP_3 receptors [68,69,70]. Calcium channel blockers have demonstrated neuroprotective effects in vitro and in animal models [71]. Elevated Ca^{2+} enhances amyloidogenic APP processing and interacts with Aβ-bound metals (Cu, Zn, Fe), facilitating redox cycling and neurotoxicity [68,72]. This cascade impairs mitochondrial ATP production, disrupts membrane potential, and activates signaling proteins such as calcineurin and calmodulin [73].

L-type calcium channels (LTCCs) are recognized as important drug targets, and several LTCC inhibitors are already in clinical use [74]. LTCC blockers (e.g., nimodipine, nifedipine, verapamil) prevent excessive calcium influx, attenuate excitotoxicity, and mitigate Aβ-induced dysregulation. Although primarily prescribed for cardiovascular disorders, these agents also demonstrate neuroprotective potential in Alzheimer's disease (AD), Parkinson's disease, and Huntington's disease [75,76]. Environmental factors including ozone-rich air pollutants, neurotoxic metals, pesticides, and fine particulate matter exacerbate AD pathology [76–78]. The contribution of carbon dioxide to AD pathogenesis, however, remains an unaddressed yet potentially significant avenue for investigation.

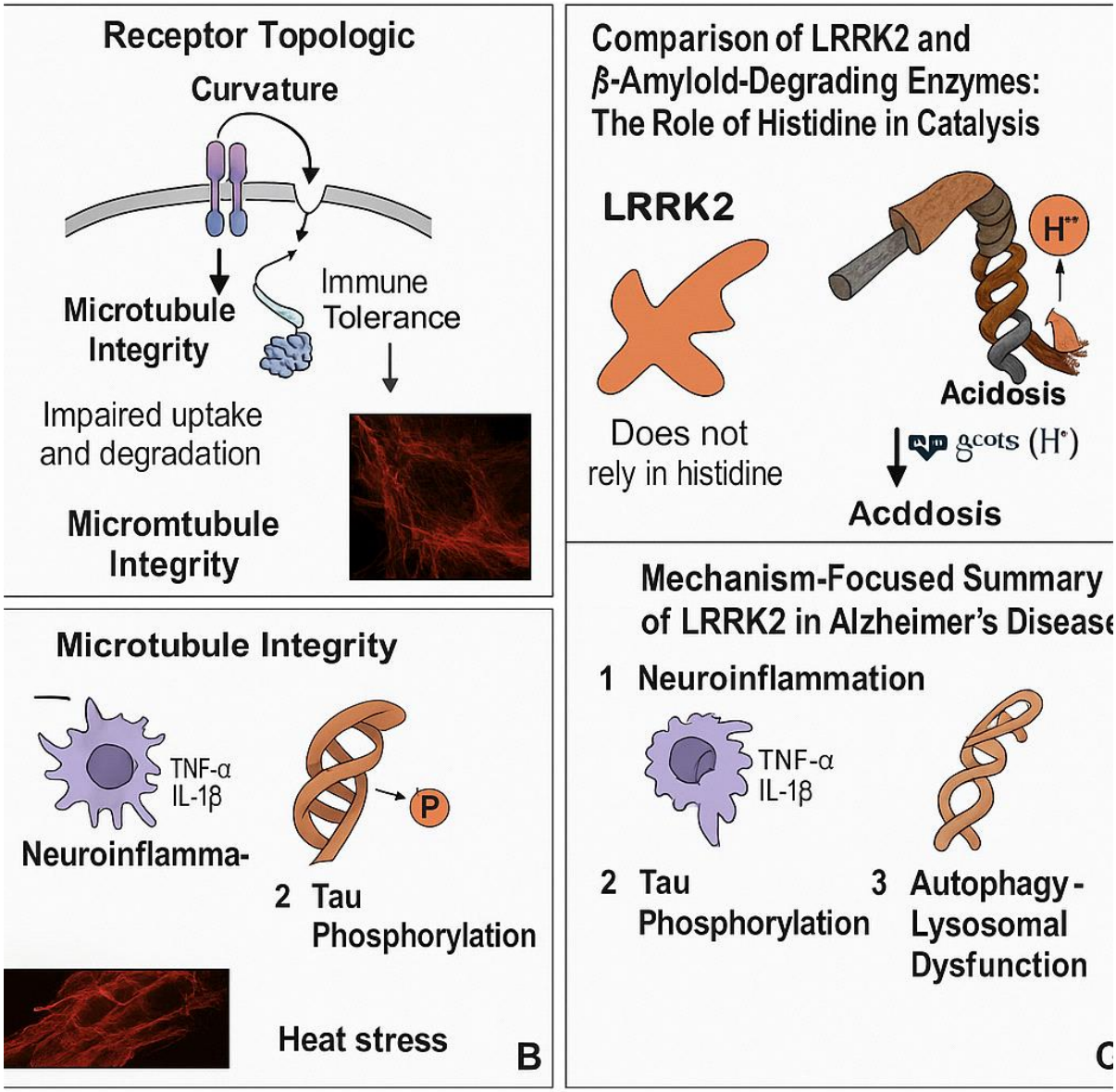

Figure 4: Mechanistic Links Between LRRK2 Function, Microtubule Integrity, and Alzheimer's Disease Pathology.

Summary: The interplay between CO_2, intracellular Ca^{2+} signaling, microtubule stability, and proteolytic enzyme activity forms a complex, interdependent framework driving Alzheimer's disease (AD) pathogenesis. Intracellular Ca^{2+} homeostasis, maintained by Ca^{2+} binding proteins, voltage-gated calcium channels (VGCCs), pumps, transporters, and intracellular stores are critical for neuronal function, while its disruption impairs mitophagy, promotes oxidative stress, and triggers mitochondrial dysfunction. Calcium dysregulation not only enhances amyloidogenic APP processing and amyloid-β (Aβ) accumulation but also exacerbates Aβ toxicity through disrupted signaling pathways and reactive oxygen species (ROS) overproduction. These effects may manifest more prominently at the neural network level than in isolated neurons, underscoring the importance of targeting network-level calcium dysfunction. Addressing this multimechanistic web offers a promising therapeutic avenue to improve treatment efficacy and potentially slow or reverse disease progression.

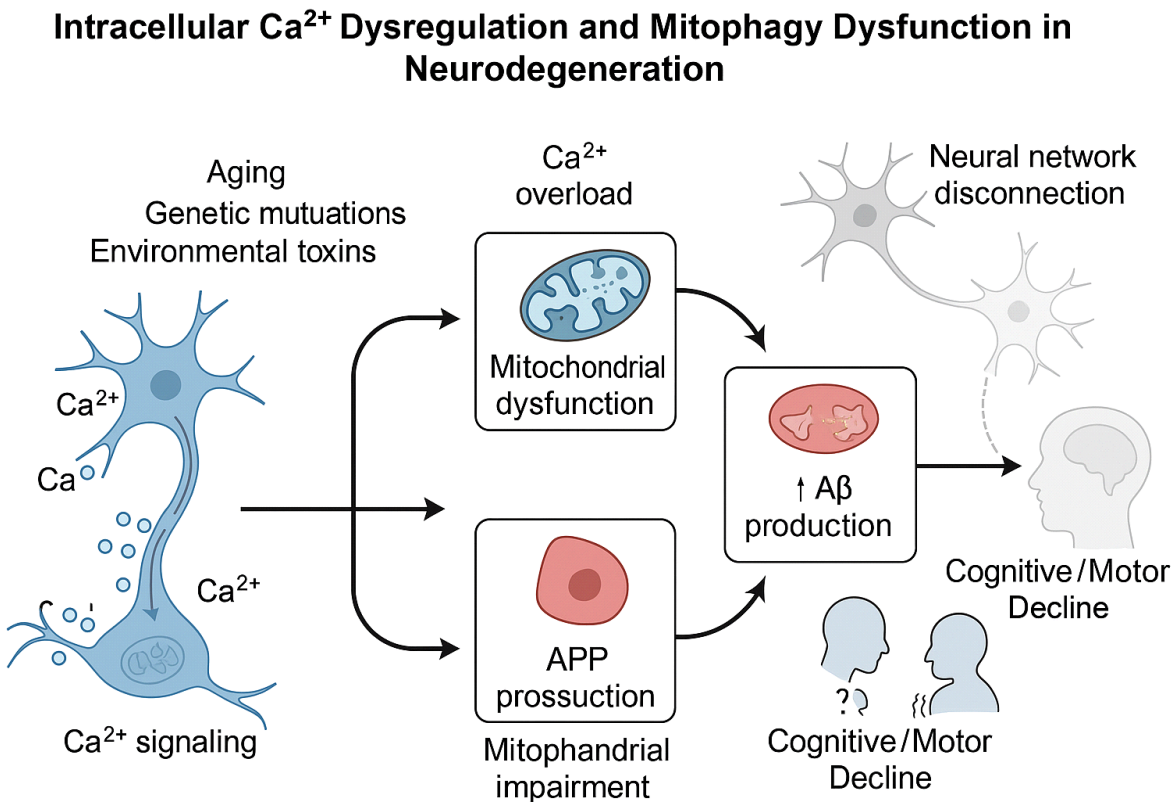

Figure 5: Role of Ca^{2+} Dysregulation and Mitophagy Impairment in Neurodegenerative Disease Progression.

CONCLUSION

The global incidence of neurodegenerative disorders has risen significantly in recent decades, now affecting approximately 15% of the population and constituting a major cause of disability. This trend parallels increasing environmental threats from carbon dioxide (CO_2) emissions and climate change. This study proposes a novel mechanistic link between CO_2 exposure and neurodegeneration, particularly Alzheimer's disease based on CO_2's unique physicochemical properties and its impact on Ca^{2+} signaling. CO_2-induced acidification disrupts β-amyloid–clearing enzymes while sparing LRRK2, a neurodegeneration-associated protein less dependent on histidine for catalytic activity. Elevated temperatures further destabilize neuronal microtubules. The interplay between CO_2, intracellular Ca^{2+} signaling, microtubule stability, and proteolytic enzyme activity constitutes a complex, interdependent framework driving AD pathogenesis. Moreover, dysregulation of intracellular Ca^{2+} homeostasis contributes to amyloid accumulation, mitochondrial dysfunction, and oxidative stress—key hallmarks of neurodegenerative disease**.** This emerging model highlights CO_2 as a potential environmental driver of calcium dysregulation and neuronal damage.

Table 4: Conclusive Summary of Mechanisms Involved in CO_2-Mediated Alzheimer's Development

Direct Effect	Thermo-Acidotic Effect	Calcium Homeostasis Effect
1. CO_2 exerts a "drill-like" action, forcing Ca^{2+} into cells. The resulting intracellular Ca^{2+} influx amplifies second messenger signaling triggered immediately upon CO_2 entry.	**1.** CO_2 inhibits β-amyloid–degrading enzymes while preserving LRRK2 kinase activity, which promotes abnormal tau phosphorylation and contributes to neurofibrillary tangle formation. It also affects microtubule integrity via thermal effects.	**1.** Calcium signaling influences APP processing, leading to increased Aβ production. It indirectly enhances Aβ toxicity by disrupting intracellular signaling. Ca^{2+} overload induces mitochondrial dysfunction and ROS generation.
2. CO_2-induced heating reversibly alters plasma membrane electrical capacitance, depolarizing target cells, activating thermosensitive ion channels, and forming membrane pores that increase conductance and trigger second messenger activation.	**2.** The acidic medium causes histidine protonation, leading to conformational changes, increased production of intracellular second messengers (e.g., cAMP), and altered subcellular receptor topologies in response to mechanical forces and thermally induced membrane fluctuations. This inhibits cellular uptake and degradation of Aβ oligomers, impairing their immune clearance.	**2.** Specialized Ca^{2+} channels known as STIMs function as sensors of decreased Ca^{2+} levels, elevated temperatures, and acidosis.
3. Acting as a second messenger, CO_2 alters the expression of immune tolerance genes that play critical roles in neurodegenerative immune responses.	**3.** The acidic environment modulates signaling cascades and Ca^{2+}-dependent transcription factors that regulate gene activity.	**3.** Ca^{2+} channel dysfunction increases cytosolic Ca^{2+} levels, promoting amyloidogenic APP cleavage and increasing Aβ availability for aggregation. Ca^{2+} overload also triggers mitochondrial dysfunction.
4. CO_2 functions as a central signaling hub in gene transcription and cytokine regulation.	**4.** The Ca^{2+} channels STIM1 and Orai1, which sense temperature and acidosis, enhance autophagy under CO_2 influence [79]. This supports the survival of self-reactive B cells by helping them evade autoimmune checkpoints.	**4.** The interplay between Ca^{2+} regulation and mitophagy is a pivotal factor in the pathogenesis of numerous neurodegenerative diseases (NDs).

	Additionally, thermal effects induce membrane curvature and fluidity, resulting in topographical changes and mobilization of membrane-bound molecules.	

Mediators involved: signaling pathways, Ca^{2+} channels, genes, second messengers, receptors, interleukins, and cytokines.

Future Directions: Mechanistic Insights and Therapeutic Opportunities

1. Emerging evidence implicates CO_2 as an environmental driver of Alzheimer's disease (AD) and other neurodegenerative disorders by disrupting Ca^{2+} signaling and neuronal integrity. Future studies should identify CO_2-responsive genes and delineate mechanisms linking CO_2 exposure to amyloid precursor protein (APP) processing, amyloid-β (Aβ) deposition, and neuroinflammation. Translational efforts should target normalization of Ca^{2+} signaling, restriction of intracellular CO_2 buildup, and preservation of neuronal networks.
2. Defining the role of CO_2 in Alzheimer's pathogenesis is critical for advancing therapeutic strategies to counter intracellular accumulation. Approaches may include limiting CO_2 diffusion, enhancing clearance, or applying hyperbaric oxygen therapy to neutralize its toxic effects. These strategies hold potential for pharmaceutical development aimed at preventing disease progression through sustained CO_2 reduction.
3. Therapeutic targeting of Ca^{2+} channels in neurodegeneration demands precision to ensure specificity and minimize off-target effects. A detailed understanding of agent–channel interactions is required to reduce cross-reactivity, prevent tissue injury, and optimize efficacy.
4. This work highlights unresolved questions concerning ion channel regulation, signaling cascades, and receptor protein alterations. These mechanisms represent promising targets for mitigating downstream pathology in neurodegenerative disease.

ABBREVIATIONS

CSF = Cerebrospinal Fluid

PET = Positron Emission Tomography

Aβ = Amyloid Beta

APP = Amyloid Precursor Protein

NFTs = Neurofibrillary Tangles

NF-κB = Nuclear Factor-kappa B.

NLRP3 = NOD-, LRR- and Pyrin domain-containing protein 3

LRRK2 = Leucine-Rich Repeat Kinase 2

IDE = Insulin-Degrading Enzyme

NEP = Neprilysin

ECE = Endothelin-Converting Enzyme

MMPs = Matrix Metalloproteinases

VGCCs = Voltage-Gated Calcium Channels

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Disclosure of Conflict of Interest

The authors declare that they have no known competing financial interests that could have influenced the work reported in this paper.

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