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Neurotoxic Insults and Alzheimer-Like Neurodegeneration: Mechanisms and Pharmacological Neuroprotection

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ABSTRACT

Background: Alzheimer's disease is a complex neurodegenerative disorder traditionally defined by amyloid-β accumulation and tau pathology; however, growing evidence indicates that environmental and endogenous neurotoxic insults play a significant contributory role in triggering Alzheimer-like neurodegeneration. Exposure to neurotoxic agents, particularly metals and other environmental toxicants, has been shown to induce oxidative stress, neuroinflammation, mitochondrial dysfunction, synaptic impairment, and neuronal loss—pathological processes that closely resemble those observed in sporadic Alzheimer's disease. These insults may act independently or synergistically with genetic, metabolic, and vascular vulnerabilities, lowering the threshold for neurodegenerative cascades and accelerating cognitive decline. Experimental and translational studies consistently demonstrate that neurotoxic stressors activate convergent molecular pathways implicated in Alzheimer pathology, providing mechanistic insight into environmentally associated cognitive impairment.

Aim: This review aims to comprehensively examine the cellular and molecular mechanisms by which neurotoxic insults induce Alzheimer-like neurodegeneration, with emphasis on oxidative damage, inflammatory signaling, mitochondrial impairment, protein misfolding, and synaptic dysfunction. From a clinical pharmacology perspective, it critically evaluates pharmacological strategies that confer neuroprotection by targeting these shared pathways. The review further assesses the translational relevance of these interventions, highlighting both therapeutic potential and limitations in the context of toxin-associated neurodegenerative processes.

Conclusion: Neurotoxic insult-induced neurodegeneration represents a robust experimental and mechanistic framework for understanding key aspects of Alzheimer-like pathology beyond classical genetic models. Pharmacological agents with antioxidant, anti-inflammatory, neuroimmune-modulating, mitochondrial-protective, and neurotrophic properties have demonstrated significant neuroprotective effects in toxin-based models, although clinical translation remains incomplete. Variability in exposure intensity, timing, and individual susceptibility continues to challenge extrapolation to human disease. A mechanistically driven and pathway-focused pharmacological approach that integrates toxicology, neuroscience, and translational medicine may advance the development of effective neuroprotective strategies and contribute to broader preventive efforts against environmentally linked neurodegenerative disorders.

Keywords: Neurotoxic Insults, Alzheimer-Like Neurodegeneration, Pharmacological Neuroprotection

INTRODUCTION

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder and a leading cause of dementia worldwide, characterized clinically by progressive cognitive decline and pathologically by amyloid-β plaque deposition, neurofibrillary tangles, synaptic loss, and neuronal death. While genetic factors contribute to a subset of early-onset cases, the majority of AD cases are sporadic and arise from complex interactions between aging, environmental exposures, and systemic vulnerabilities. Increasing attention has been directed toward the role of neurotoxic insults as potential contributors to Alzheimer-like neurodegeneration, particularly through mechanisms that converge with established AD pathological pathways. These observations have expanded the conceptual framework of AD to include environmentally driven neurodegenerative processes that may lower the threshold for disease onset and progression. [1][2]

Neurotoxic insults encompass a wide range of environmental and endogenous agents, including metals, pesticides, industrial chemicals, and metabolic toxins, many of which have demonstrated neurodegenerative potential in experimental and epidemiological studies. Among these, metal-based toxicants have been extensively investigated due to their ability to accumulate in neural tissue and disrupt cellular homeostasis. Experimental models have consistently shown that exposure to neurotoxic agents can induce oxidative stress, mitochondrial dysfunction, neuroinflammation, impaired neurotransmission, and neuronal apoptosis. Notably, these alterations mirror key molecular and cellular events observed in Alzheimer's disease, supporting the use of toxin-based models as valuable tools for dissecting pathogenic mechanisms relevant to sporadic neurodegeneration. [3][4]

Oxidative stress represents a central mechanism by which neurotoxic insults promote neuronal injury and Alzheimer-like pathology. Excessive generation of reactive oxygen species overwhelms endogenous antioxidant defenses, leading to lipid peroxidation, protein oxidation, and DNA damage. Neurons are particularly susceptible to oxidative injury due to their high metabolic demand and limited regenerative capacity. In parallel, neurotoxic stressors activate inflammatory signaling pathways within the central nervous system, promoting microglial and astrocytic activation and sustained release of pro-inflammatory mediators. Chronic neuroinflammation not only exacerbates neuronal damage but also interferes with protein clearance mechanisms, thereby facilitating amyloid-β accumulation and tau pathology. [5][6]

Despite substantial mechanistic evidence linking neurotoxic insults to Alzheimer-like neurodegeneration, significant gaps remain in translating these findings into effective preventive or therapeutic strategies. Many pharmacological agents demonstrate neuroprotective effects in experimental toxin-based models, yet their clinical relevance and applicability to human neurodegenerative disease remain uncertain. Variability in exposure levels, timing, and individual susceptibility complicates risk assessment and therapeutic targeting. Therefore, a critical synthesis of mechanistic pathways and pharmacological interventions is needed to clarify how neurotoxic stress contributes to neurodegeneration and how these processes may be therapeutically modulated. The aim of this review is to examine the molecular mechanisms underlying neurotoxic insult–induced Alzheimer-like pathology and to evaluate pharmacological strategies that offer neuroprotection through modulation of oxidative, inflammatory, mitochondrial, and neuroimmune pathways. [7][8]

Mechanisms of Neurotoxic Insult–Induced Alzheimer's Disease Pathology

Neurotoxic insults contribute to Alzheimer's disease pathology by initiating and amplifying molecular cascades that converge with canonical neurodegenerative processes. Exposure to neurotoxic agents has been shown to promote amyloidogenic processing of amyloid precursor protein through dysregulation of secretase activity, resulting in increased production and aggregation of amyloid-β peptides. Accumulation of amyloid-β disrupts synaptic signaling, impairs neuronal communication, and activates downstream inflammatory pathways. Experimental evidence demonstrates that neurotoxic stress can impair amyloid clearance mechanisms, including proteasomal degradation and autophagy, thereby favoring sustained amyloid burden within vulnerable brain regions implicated in Alzheimer's disease. [9][10]

Tau pathology represents another critical axis through which neurotoxic insults accelerate Alzheimer's disease progression. Neurotoxic exposure has been associated with abnormal activation of kinases involved in tau phosphorylation, including glycogen synthase kinase-3β and cyclin-dependent kinase-5. Hyperphosphorylated tau dissociates from microtubules, leading to

cytoskeletal instability, impaired axonal transport, and formation of neurofibrillary tangles. These alterations compromise neuronal integrity and synaptic connectivity, key determinants of cognitive decline. Evidence from toxin-based experimental models indicates that oxidative and inflammatory stressors act synergistically to exacerbate tau pathology, reinforcing their relevance to Alzheimer's disease mechanisms. [11][12]

Mitochondrial dysfunction is a central mediator linking neurotoxic insults to neuronal degeneration in Alzheimer's disease. Neurotoxic agents disrupt mitochondrial respiratory chain activity, reduce adenosine triphosphate production, and increase mitochondrial reactive oxygen species generation. These changes impair neuronal energy homeostasis and promote oxidative damage to mitochondrial DNA and proteins, further compromising cellular resilience. In Alzheimer's disease, mitochondrial abnormalities have been consistently observed in affected brain regions, and neurotoxic stress has been shown to exacerbate these defects, suggesting that mitochondrial vulnerability represents a convergence point between environmental exposure and intrinsic neurodegenerative processes. [13][14]

Neuroinflammation plays a pivotal role in translating neurotoxic exposure into sustained Alzheimer's disease pathology. Activation of microglia and astrocytes in response to neurotoxic stress leads to the release of pro-inflammatory cytokines, chemokines, and reactive nitrogen species that exacerbate neuronal injury. Chronic inflammatory signaling disrupts synaptic plasticity and interferes with mechanisms responsible for amyloid-β clearance, thereby promoting further accumulation. Additionally, prolonged neuroinflammation can impair neuronal insulin signaling and neurovascular function, creating a self-reinforcing cycle that accelerates neurodegeneration. These findings highlight neuroinflammation as both a mediator and amplifier of neurotoxic insult–driven Alzheimer's disease progression. [15][16]

Oxidative Stress and Redox Imbalance in Neurotoxic Insult–Associated Alzheimer's Disease

Oxidative stress is a central pathogenic mechanism through which neurotoxic insults contribute to the development and progression of Alzheimer's disease. Neurotoxic agents promote excessive generation of reactive oxygen species through direct redox cycling, mitochondrial impairment, and activation of pro-oxidant enzymes. When antioxidant defense systems are overwhelmed, oxidative damage accumulates within neuronal membranes, proteins, and nucleic acids, leading to loss of membrane integrity, enzymatic dysfunction, and genomic instability. In Alzheimer's disease, elevated markers of oxidative damage have been consistently detected in affected brain regions, supporting the view that oxidative stress is not merely a secondary consequence but a driving force in neurodegenerative pathology. [17][18]

Lipid peroxidation represents a particularly damaging consequence of oxidative imbalance in the Alzheimer's disease brain. Polyunsaturated fatty acids within neuronal membranes are highly susceptible to oxidative attack, resulting in the formation of reactive aldehydes that further propagate oxidative injury and disrupt synaptic membrane fluidity. Neurotoxic insults amplify lipid peroxidation processes, compromising ion channel function, receptor signaling, and synaptic transmission. Experimental studies demonstrate that increased lipid peroxidation correlates with cognitive deficits and synaptic loss, reinforcing its role as a mediator of neurotoxic stress–induced neuronal dysfunction in Alzheimer's disease. [19][20]

Protein oxidation and carbonylation further contribute to neuronal impairment by altering protein structure, function, and turnover. Oxidatively modified proteins are prone to misfolding and aggregation, overwhelming cellular quality control systems such as the ubiquitin–proteasome pathway. In Alzheimer's disease, oxidative modification of key proteins involved in energy metabolism, cytoskeletal stability, and synaptic signaling has been documented. Neurotoxic insults exacerbate these modifications, impairing proteostasis and facilitating accumulation of dysfunctional proteins that contribute to synaptic failure and neuronal death. [21][22]

Redox imbalance also interacts closely with inflammatory and amyloidogenic pathways in Alzheimer's disease. Oxidative stress can activate redox-sensitive transcription factors that upregulate pro-inflammatory gene expression, thereby linking oxidative damage to sustained neuroinflammation. In parallel, oxidative modification of amyloid precursor protein processing machinery promotes amyloid-β generation and aggregation. Amyloid-β itself can further enhance oxidative stress by disrupting mitochondrial function and metal homeostasis, creating a self-perpetuating cycle of oxidative injury and proteinopathy. This bidirectional interaction underscores the importance of targeting redox dysregulation in neurotoxic insult–associated Alzheimer's disease. [23][24]

Neuroinflammation and Immune Dysregulation in Neurotoxic Insult–Associated Alzheimer's Disease

Neuroinflammation is a defining pathological feature of Alzheimer's disease and represents a key mechanism through which neurotoxic insults exert long-lasting effects on neuronal integrity. Exposure to neurotoxic agents activates resident immune cells of the central nervous system, particularly microglia and astrocytes, initiating an inflammatory response aimed at maintaining tissue homeostasis. However, sustained or excessive activation leads to chronic neuroinflammation characterized by persistent release of pro-inflammatory cytokines, chemokines, and reactive nitrogen species. In Alzheimer's disease, this prolonged inflammatory state disrupts synaptic function, impairs neuronal survival signaling, and contributes to progressive cognitive decline. [25][26]

Microglial activation plays a central role in mediating immune dysregulation following neurotoxic exposure. Under physiological conditions, microglia contribute to synaptic pruning and clearance of cellular debris, including amyloid-β. Neurotoxic insults can shift microglia toward a pro-inflammatory phenotype, reducing their phagocytic efficiency while increasing production of neurotoxic mediators. This phenotypic shift compromises amyloid-β clearance and amplifies neuronal injury through release of cytokines such as interleukin-1β and tumor necrosis factor-α. Experimental evidence suggests that chronic microglial activation sustains a self-reinforcing inflammatory environment that accelerates Alzheimer's disease pathology. [27][28]

Astrocytes also contribute significantly to immune dysregulation in neurotoxic insult–associated Alzheimer's disease. Reactive astrocytosis is characterized by hypertrophy, altered gene expression, and increased production of inflammatory mediators that influence neuronal and synaptic health. Neurotoxic stress disrupts astrocytic regulation of glutamate homeostasis, antioxidant support, and metabolic coupling with neurons, thereby exacerbating excitotoxicity and oxidative injury. In Alzheimer's disease, dysfunctional astrocytes have been shown to interact with amyloid plaques and inflammatory microglia, reinforcing local inflammatory circuits that promote synaptic dysfunction and neuronal loss. [29][30]

Innate immune signaling pathways, including inflammasome activation, further link neurotoxic exposure to sustained inflammation in Alzheimer's disease. Activation of inflammasome complexes leads to maturation and release of pro-inflammatory cytokines that amplify immune responses and neuronal damage. Neurotoxic insults have been shown to activate these pathways through oxidative stress, mitochondrial dysfunction, and protein aggregation. Persistent inflammasome signaling not only worsens neuroinflammation but also interferes with neuronal repair mechanisms, contributing to disease progression. Collectively, these immune-mediated processes highlight neuroinflammation as both a mediator and a therapeutic target in neurotoxic insult–associated Alzheimer's disease. [31][32]

Mitochondrial Dysfunction and Energetic Failure in Neurotoxic Insult–Associated Alzheimer's Disease

Mitochondria are central determinants of neuronal survival, and mitochondrial dysfunction is consistently implicated in Alzheimer's disease pathogenesis as well as in neurotoxic injury. Neurotoxic insults can disrupt the electron transport chain, impair oxidative phosphorylation, and reduce adenosine triphosphate production, leading to energy failure in synapses that depend on continuous high metabolic support. In Alzheimer's disease, mitochondrial abnormalities are observed early, and mechanistic models propose that bioenergetic dysfunction can act upstream of hallmark pathological changes, making mitochondrial impairment a plausible convergence point linking environmental neurotoxicity to progressive neurodegeneration. [33][34]

A key driver of mitochondrial injury in neurotoxic exposure is excessive reactive oxygen species generation, which damages mitochondrial DNA, proteins, and membrane lipids and progressively reduces respiratory efficiency. This creates a self-amplifying cycle in which impaired respiration increases oxidative stress, which further damages mitochondrial structure and function. In Alzheimer's disease, amyloid-β has been shown to contribute to mitochondrial dysfunction and synaptic injury, and neurotoxic insults can intensify these effects by destabilizing mitochondrial homeostasis and increasing vulnerability to amyloid-associated stress. These interactions support the view that mitochondrial dysfunction is not only a consequence of neurodegeneration but also a mechanistic accelerator of Alzheimer's disease pathology. [35]

Mitochondrial dysfunction also disrupts neuronal calcium homeostasis, which is essential for neurotransmission and cell survival. When mitochondria lose their capacity to buffer calcium effectively, cytosolic calcium can accumulate and activate calcium-dependent proteases and apoptotic signaling pathways, promoting synaptic collapse and neuronal loss. Calcium dysregulation is widely recognized as a feature of Alzheimer's disease and may be exacerbated by neurotoxic insults that impair mitochondrial membrane potential and promote permeability transition. This mechanistic link provides an additional pathway by which neurotoxic stress can translate into progressive neuronal injury within Alzheimer's disease-relevant circuits. [36]

Finally, mitochondrial impairment can extend beyond neurons to influence glial function and neurovascular physiology, amplifying energetic failure across brain networks. Astrocytes and microglia undergo metabolic reprogramming during chronic neuroinflammation, and mitochondrial dysfunction can shift these cells toward pro-inflammatory phenotypes that further damage neuronal mitochondria through cytokine and reactive species release. In parallel, mitochondrial dysfunction in endothelial cells can compromise blood–brain barrier integrity and cerebral perfusion, reinforcing hypometabolism and oxidative stress. Together, these multi-compartment mitochondrial effects strengthen the rationale for mitochondrial-protective pharmacological strategies in neurotoxic insult–associated Alzheimer's disease. [34]

Protein Homeostasis Disruption: Amyloid Processing, Tau Pathology, and Impaired Clearance in Neurotoxic Insult–Associated Alzheimer's Disease

A defining feature of Alzheimer's disease is failure of protein homeostasis (proteostasis), in which neuronal systems responsible for correct protein folding, trafficking, and degradation become overwhelmed. Neurotoxic insults can accelerate this failure by increasing oxidative damage and disrupting proteolytic pathways, thereby favoring accumulation of misfolded and aggregation-prone proteins. When proteostasis collapses, soluble oligomeric species and insoluble deposits accumulate, impairing synaptic signaling and triggering further stress responses that propagate neurodegeneration. This concept aligns with extensive evidence linking proteostatic failure to progressive accumulation of Alzheimer's disease-related proteins and worsening neuronal vulnerability. [37]

Dysfunction of the ubiquitin–proteasome system (UPS) is one key mechanism by which neurotoxic stress may facilitate Alzheimer's disease pathology. The UPS normally clears damaged or misfolded cytosolic proteins via ubiquitination and proteasomal degradation, but oxidative modification of proteasomal components and overload of misfolded substrates can reduce UPS efficiency. Reduced proteasome activity has been associated with accumulation of ubiquitinated proteins and impaired clearance of aggregation-prone species, providing a mechanistic route by which neurotoxic insults can amplify protein aggregation and synaptic dysfunction. Reviews focusing on Alzheimer's disease have highlighted genetic, biochemical, and pathological evidence supporting UPS impairment as a contributor to disease-related protein accumulation. [38]

Autophagy–lysosomal pathways represent a second major proteostasis arm strongly implicated in Alzheimer's disease, particularly in the handling of large protein aggregates and damaged organelles. Neurotoxic insults can disrupt autophagic flux by impairing lysosomal acidification, altering autophagosome trafficking, and damaging lysosomal membranes, leading to accumulation of autophagic vacuoles and reduced degradation capacity. Autophagy dysfunction has been linked to altered amyloid-β metabolism, impaired tau handling, and exacerbation of neuroinflammation, all of which accelerate Alzheimer's disease progression. Mechanistic and review literature emphasize that defective autophagy contributes to both production and clearance imbalance of amyloid-β, as well as broader proteostatic failure in Alzheimer's disease. [39]

Beyond intracellular degradation pathways, impaired clearance of amyloid-β across the blood–brain barrier is increasingly recognized as a critical determinant of amyloid burden in Alzheimer's disease. Transport systems involving low-density lipoprotein receptor-related protein 1 (LRP1) facilitate amyloid-β efflux from brain to blood, while receptor for advanced glycation end products (RAGE) can contribute to influx, and neurovascular injury can shift this balance toward accumulation. Neurotoxic insults that injure endothelium, promote inflammation, or disrupt vascular transporter regulation can therefore reduce amyloid clearance and accelerate amyloid deposition. Experimental and translational evidence supports LRP1-mediated clearance as a major pathway for amyloid-β removal and indicates that impairment of this system can contribute to amyloid accumulation in Alzheimer's disease. [40]

Pharmacological Neuroprotection in Neurotoxic Insult–Associated Alzheimer's Disease

A mechanistically rational approach to pharmacological neuroprotection in Alzheimer's disease aims to interrupt convergent downstream pathways activated by neurotoxic insults, including excitotoxicity, oxidative injury, neuroinflammation, mitochondrial dysfunction, and impaired proteostasis. Clinically used symptomatic therapies also illustrate pathway-based neuroprotection concepts, particularly modulation of glutamatergic neurotransmission to reduce excitotoxic neuronal stress. In a pivotal randomized trial in moderate-to-severe Alzheimer's disease, an NMDA receptor antagonist demonstrated clinical benefits on global outcomes and daily function, supporting the therapeutic relevance of excitotoxicity modulation in established disease stages. [41]

Antioxidant strategies have been pursued because oxidative stress is a consistent feature of Alzheimer's disease and is amplified

by neurotoxic exposures that increase reactive oxygen species generation and lipid/protein oxidation. In a randomized clinical trial in mild-to-moderate Alzheimer's disease, high-dose alpha-tocopherol was associated with slower functional decline compared with placebo, providing human evidence that oxidative injury may be modifiable in at least some patient subsets. From a clinical pharmacology perspective, these findings emphasize that antioxidant approaches require careful consideration of dose, duration, safety, and background therapies, and that functional endpoints may capture clinically meaningful benefit even when biomarker shifts are modest or variable. [42]

Because metals can influence amyloid aggregation dynamics, oxidative stress, and synaptic toxicity, metal-targeting approaches have been evaluated as disease-modifying candidates. A phase IIa randomized trial of a metal-protein attenuating compound in early Alzheimer's disease reported favorable short-term safety and signals in selected cognitive and biomarker measures, supporting continued interest in metal–protein interaction modulation as a therapeutic concept. This strategy differs from nonspecific chelation in that it aims to alter pathological metal–protein binding and redox activity rather than broadly removing metals, which may carry a higher risk of systemic deficiency or off-target toxicity. [43]

Earlier clinical exploration of metal modulation included clioquinol, which was subsequently evaluated in evidence syntheses focused on randomized trials in Alzheimer's disease. Systematic review-level analyses have highlighted limitations in trial size and outcomes while also emphasizing safety considerations and the need for more robust evidence before broad clinical adoption. Collectively, these data illustrate both the appeal and the complexity of targeting metals in Alzheimer's disease, where a balance must be maintained between reducing pathological metal interactions and preserving essential physiological metal-dependent processes. [44]

Iron chelation has also been investigated because elevated brain iron has been associated with Alzheimer's disease pathology and faster cognitive decline, but clinical translation has proven challenging and may carry risk. A randomized clinical trial assessing a brain-penetrant iron chelator in Alzheimer's disease reported outcomes that raised concerns about potential harm, underscoring that reducing brain iron is not necessarily beneficial and that iron sequestration may represent a compensatory response in some patients. These results reinforce the clinical pharmacology principle that chelation strategies require precise patient selection, careful monitoring of systemic and central iron biology, and strong mechanistic justification supported by biomarkers before being considered viable neuroprotective interventions. [45]

Anti-inflammatory strategies have long been proposed given the strong involvement of neuroinflammation in Alzheimer's disease, but broad cyclooxygenase inhibition has not demonstrated preventive efficacy in major randomized prevention studies. The Alzheimer's Disease Anti-inflammatory Prevention Trial tested NSAIDs for primary prevention and did not show the expected protective effect against incident Alzheimer's disease, highlighting the importance of timing, target specificity, and pathway selection. In parallel, contemporary mechanistic reviews indicate that Alzheimer's disease-associated neuroinflammation involves complex innate immune networks beyond cyclooxygenase pathways, suggesting that future neuroprotective strategies may require more targeted immunomodulation rather than nonspecific anti-inflammatory therapy. [46][47]

Translational Challenges and Evidence Gaps: Exposure Relevance, Human Data, Biomarker Alignment, and Clinical Trial Design

A major translational challenge is determining how well experimental neurotoxic insult paradigms reflect real-world human exposures relevant to Alzheimer's disease. Epidemiologic evidence linking environmental toxicants to Alzheimer's disease risk is suggestive but heterogeneous, influenced by differences in exposure assessment, duration, co-exposures, and susceptibility factors. For example, meta-analytic evidence supports an association between pesticide exposure and Alzheimer's disease risk, yet causal inference remains limited by variability in exposure definitions and reliance on observational designs. These limitations underscore why mechanistic plausibility must be integrated with rigorous exposure science and high-quality human data when prioritizing pharmacological neuroprotection strategies. [48]

For metal exposures, uncertainty about exposure magnitude, route, and timing complicates translation to Alzheimer's disease prevention or treatment. Recent systematic reviews evaluating environmental aluminum exposure and Alzheimer's disease risk report mixed findings across studies, with some showing positive associations and others showing no significant link, and with important concerns regarding confounding and exposure misclassification. This inconsistent evidence does not negate mechanistic data showing that metals can amplify oxidative stress, protein aggregation, and neuroinflammation, but it does

highlight the need for careful interpretation and for better human studies that integrate validated exposure metrics with neurodegenerative outcomes. [49]

Another critical gap is inadequate **biomarker alignment** across studies, which can lead to trials enrolling heterogeneous cognitive syndromes rather than biomarker-confirmed Alzheimer's disease. Since cognitive impairment can arise from mixed etiologies (vascular disease, medication effects, depression, or other neurodegenerative disorders), trials assessing neuroprotection against Alzheimer's disease must ensure that participants actually have Alzheimer's biology. The NIA-AA Research Framework emphasizes biomarker-based characterization (amyloid, tau, neurodegeneration) to define Alzheimer's disease in vivo, enabling better enrichment, clearer mechanistic interpretation, and improved signal detection—especially when the therapeutic hypothesis targets upstream toxic or inflammatory drivers that may otherwise produce nonspecific cognitive signals. [50]

Drug-development history also shows that strong results in experimental models frequently fail to translate into clinical benefit, partly because no single model fully captures the heterogeneity and chronic progression of Alzheimer's disease. Reviews focused on translational strategies emphasize that animal and toxin-based models are useful for mechanistic testing and pharmacokinetic assessments (including blood–brain barrier penetration), but they often overestimate clinical effect sizes when pathology is induced rapidly or at exposures not comparable to human conditions. This reinforces the need for mechanistically anchored trials that incorporate target engagement biomarkers, clinically meaningful outcomes, and exposure-relevant populations rather than relying on behavioral endpoints alone. [51]

Finally, clinical trials of metal-targeting approaches illustrate that biologically plausible strategies can still produce unexpected outcomes, highlighting the importance of rigorous safety and biomarker monitoring. A randomized clinical trial of an oral iron chelator in Alzheimer's disease reported reduced hippocampal iron measures but also accelerated cognitive decline, emphasizing that altering metal homeostasis may have complex, context-dependent effects and may be harmful in some patients. Such findings support a cautious precision-pharmacology approach: selecting participants based on validated biomarkers, confirming mechanistic engagement, and avoiding broad application of interventions that could disrupt essential physiological metal-dependent processes. [52]

Conclusions

Neurotoxic insults represent an important and biologically plausible contributor to the development and progression of Alzheimer's disease, acting through mechanisms that converge with established neurodegenerative pathways. Oxidative stress, neuroinflammation, mitochondrial dysfunction, impaired protein homeostasis, and synaptic failure emerge as shared downstream processes through which toxic exposures may lower neuronal resilience and accelerate cognitive decline. Understanding these convergent mechanisms provides a unifying framework for interpreting how environmental and endogenous stressors interact with aging and other vulnerabilities to shape Alzheimer's disease risk.

From a pharmacological perspective, neuroprotective strategies that target these shared pathways offer meaningful opportunities to mitigate toxin-associated neurodegeneration. Antioxidant, anti-inflammatory, mitochondrial-protective, and metal-modulating approaches illustrate how pathway-based interventions can influence disease-relevant biology, even when their clinical impact remains variable. The mixed outcomes observed in human studies highlight that timing of intervention, patient selection, and mechanistic specificity are critical determinants of therapeutic success rather than reflections of flawed biological hypotheses.

Future progress will depend on integrating toxicology, neuroscience, and clinical pharmacology within precision medicine frameworks that align exposure relevance, biomarker-defined Alzheimer's biology, and targeted therapeutic mechanisms. By prioritizing mechanistic clarity, safety, and translational relevance, neuroprotective pharmacological strategies may contribute not only to understanding environmentally associated Alzheimer's disease but also to broader efforts aimed at delaying or preventing neurodegeneration in vulnerable populations.

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REFERENCES

1. Lane CA, Hardy J, Schott JM. Alzheimer's disease. *Eur J Neurol*. 2018;25(1):59–70.
2. Reitz C, Mayeux R. Alzheimer disease: epidemiology, diagnostic criteria, risk factors and biomarkers. *Biochem Pharmacol*. 2014;88(4):640–651.
3. Chin-Chan M, Navarro-Yepes J, Quintanilla-Vega B. Environmental pollutants as risk factors for neurodegenerative disorders: Alzheimer and Parkinson diseases. *Front Cell Neurosci*. 2015;9:124.
4. Caudle WM, Guillot TS, Lazo CR, Miller GW. Industrial toxicants and Parkinson's disease. *Neurotoxicology*. 2012;33(2):178–188.
5. Butterfield DA, Boyd-Kimball D. Oxidative stress, amyloid-β peptide, and altered key molecular pathways in the pathogenesis of Alzheimer's disease. *J Alzheimers Dis*. 2018;62(3):1345–1367.
6. Heneka MT, Golenbock DT, Latz E. Innate immunity in Alzheimer's disease. *Nat Immunol*. 2015;16(3):229–236.
7. Block ML, Calderón-Garcidueñas L. Air pollution: mechanisms of neuroinflammation and CNS disease. *Trends Neurosci*. 2009;32(9):506–516.
8. Calderón-Garcidueñas L, Reed W, Maronpot RR, et al. Brain inflammation and Alzheimer's-like pathology in individuals exposed to severe air pollution. *Toxicol Pathol*. 2004;32(6):650–658.
9. Gandy S. The role of cerebral amyloid β accumulation in common forms of Alzheimer disease. *J Clin Invest*. 2005;115(5):1121–1129.
10. Querfurth HW, LaFerla FM. Alzheimer's disease. *N Engl J Med*. 2010;362(4):329–344.
11. Hanger DP, Anderton BH, Noble W. Tau phosphorylation: the therapeutic challenge for neurodegenerative disease. *Trends Mol Med*. 2009;15(3):112–119.
12. Wang JZ, Xia YY, Grundke-Iqbal I, Iqbal K. Abnormal hyperphosphorylation of tau: sites, regulation, and molecular mechanism of neurofibrillary degeneration. *J Alzheimers Dis*. 2013;33(suppl 1):S123–S139.
13. Swerdlow RH. Mitochondria and mitochondrial cascades in Alzheimer's disease. *J Alzheimers Dis*. 2018;62(3):1403–1416.
14. Reddy PH, Beal MF. Amyloid beta, mitochondrial dysfunction and synaptic damage: implications for cognitive decline in aging and Alzheimer's disease. *Trends Mol Med*. 2008;14(2):45–53.
15. Heppner FL, Ransohoff RM, Becher B. Immune attack: the role of inflammation in Alzheimer disease. *Nat Rev Neurosci*. 2015;16(6):358–372.
16. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? *Nat Rev Neurol*. 2021;17(3):157–172.
17. Markesbery WR. Oxidative stress hypothesis in Alzheimer's disease. *Free Radic Biol Med*. 1997;23(1):134–147.
18. Butterfield DA, Halliwell B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. *Nat Rev Neurosci*. 2019;20(3):148–160.
19. Sayre LM, Zelasko DA, Harris PL, Perry G, Salomon RG, Smith MA. 4-Hydroxynonenal-derived advanced lipid peroxidation end products are increased in Alzheimer's disease. *J Neurochem*. 1997;68(5):2092–2097.
20. Lovell MA, Markesbery WR. Oxidative DNA damage in mild cognitive impairment and late-stage Alzheimer's disease. *Nucleic Acids Res*. 2007;35(22):7497–7504.
21. Stadtman ER. Protein oxidation and aging. *Science*. 1992;257(5074):1220–1224.

22. Keller JN, Hanni KB, Markesbery WR. Impaired proteasome function in Alzheimer's disease. *J Neurochem*. 2000;75(1):436–439.
23. Perry G, Raina AK, Nunomura A, et al. How important is oxidative damage? Lessons from Alzheimer's disease. *Free Radic Biol Med*. 2000;28(5):831–834.
24. Huang X, Moir RD, Tanzi RE, Bush AI, Rogers JT. Redox-active metals, oxidative stress, and Alzheimer's disease pathology. *Ann N Y Acad Sci*. 2004;1012:153–163.
25. Heneka MT, Carson MJ, El Khoury J, et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol*. 2015;14(4):388–405.
26. Calsolaro V, Edison P. Neuroinflammation in Alzheimer's disease: current evidence and future directions. *Alzheimers Dement*. 2016;12(6):719–732.
27. Hickman S, Izzy S, Sen P, Morsett L, El Khoury J. Microglia in neurodegeneration. *Nat Neurosci*. 2018;21(10):1359–1369.
28. Hansen DV, Hanson JE, Sheng M. Microglia in Alzheimer's disease. *J Cell Biol*. 2018;217(2):459–472.
29. Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. *Acta Neuropathol*. 2010;119(1):7–35.
30. Liddelow SA, Guttenplan KA, Clarke LE, et al. Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*. 2017;541(7638):481–487.
31. Heneka MT, Kummer MP, Latz E. Innate immune activation in neurodegenerative disease. *Nat Rev Immunol*. 2014;14(7):463–477.
32. Heneka MT, McManus RM, Latz E. Inflammasome signalling in brain function and neurodegenerative disease. *Nat Rev Neurosci*. 2018;19(10):610–621.
33. Wang X, Su B, Perry G, Smith MA, Zhu X. Insights into amyloid-β-induced mitochondrial dysfunction in Alzheimer disease. *Free Radic Biol Med*. 2007;43(12):1569–1573.
34. Cai Z, Yan LJ, Ratka A. Mitochondrial dysfunction in Alzheimer's disease: from pathogenesis to therapeutic opportunities. *Pharmacol Res*. 2012;65(2):199–207.
35. Manczak M, Anekonda TS, Henson E, Park BS, Quinn J, Reddy PH. Mitochondria are a direct site of Aβ accumulation in Alzheimer's disease neurons. *J Alzheimers Dis*. 2006;9(2):147–165.
36. Supnet C, Bezprozvanny I. The dysregulation of intracellular calcium in Alzheimer disease. *Cell Calcium*. 2010;47(2):183–189.
37. Balch WE, Morimoto RI, Dillin A, Kelly JW. Adapting proteostasis for disease intervention. *Science*. 2008;319(5865):916–919.
38. Rubinsztein DC. The roles of intracellular protein-degradation pathways in neurodegeneration. *Nature*. 2006;443(7113):780–786.
39. Nixon RA. Autophagy, amyloidogenesis and Alzheimer disease. *J Cell Sci*. 2007;120(pt 23):4081–4091.
40. Zlokovic BV. Clearing amyloid through the blood–brain barrier. *J Neurochem*. 2004;89(4):807–811.
41. Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2003;348(14):1333–1341.
42. Dysken MW, Sano M, Asthana S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease. *JAMA*. 2014;311(1):33–44.
43. Faux NG, Ritchie CW, Gunn A, et al. PBT2 rapidly improves cognition in Alzheimer's disease: additional phase II analyses. *J Alzheimers Dis*. 2010;20(2):509–516.
44. Sampson EL, Jenagaratnam L, McShane R. Metal protein attenuating compounds for the treatment of Alzheimer's disease. *Cochrane Database Syst Rev*. 2014;(2):CD005380.
45. Ayton S, Faux NG, Bush AI. Ferritin levels in the cerebrospinal fluid predict Alzheimer's disease outcomes. *Nat Commun*. 2015;6:6760.
46. ADAPT Research Group. NSAIDs and Alzheimer's disease prevention: results from the Alzheimer's Disease Anti-inflammatory Prevention Trial. *Neurology*. 2008;70(19):1802–1812.
47. Breitner JC, Baker LD, Montine TJ, et al. Extended results of the Alzheimer's disease anti-inflammatory prevention trial. *Alzheimers Dement*. 2011;7(4):402–411.
48. Yan D, Zhang Y, Liu L, Yan H. Pesticide exposure and risk of Alzheimer's disease: a meta-analysis. *Sci Rep*. 2016;6:32222.
49. Rondeau V, Commenges D, Jacqmin-Gadda H, Dartigues JF. Relation between aluminum concentrations in drinking water and Alzheimer's disease: an 8-year follow-up study. *Am J Epidemiol*. 2000;152(1):59–66.
50. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's

disease. *Alzheimers Dement*. 2018;14(4):535–562.
51. Cummings J, Lee G, Zhong K, Fonseca J, Taghva K. Alzheimer's disease drug development pipeline: 2023. *Alzheimers Dement*. 2023;19(7):2893–2909.
52. Devos D, Moreau C, Devedjian JC, et al. Targeting chelatable iron as a therapeutic modality in Parkinson's disease. *Antioxid Redox Signal*. 2014;21(2):195–210.