Review

Associations of Environmental Exposure to Arsenic, Manganese, Lead and Cadmium on Alzheimer's Disease: A REVIEW OF RECENT EVIDENCE FROM MECHANISTIC STUDIES

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Review

Associations of Environmental Exposure to Arsenic, Manganese, Lead and Cadmium on Alzheimer's Disease: A Review of Recent Evidence from Mechanistic Studies

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Abstract: Numerous epidemiological studies indicate that populations exposed to environmental hazards such as heavy metals have a higher likelihood of developing Alzheimer's disease (AD) compared to those unexposed indicating a potential association between heavy metals exposure and Alzheimer's disease and related dementias (AD/ADRD). The aim of this review is to summarize contemporary mechanistic research exploring the associations of four important metals, Arsenic (As), Manganese (Mn), Lead (Pb), and Cadmium (Cd) with AD and possible pathways, processes, and molecular mechanisms on the basis of data from the most recent mechanistic studies. Primary research publications published during the last decade, were located using a search of the PubMed Database. A thorough literature search and final screening yielded 46 original research articles for this review. Of the 46 papers, 6 pertain to As, 9 to Mn, 21 to Pb, and 10 to Cd exposures and AD pathobiology. Environmental exposure to these heavy metals induce a wide range of pathological processes that intersect with well-known mechanisms of AD, such as oxidative stress, mitochondrial dysfunction, protein aggregation, and neuroinflammation, autophagy dysfunction, and Tau hyperphosphorylation. While exposure to single metals shares some affected pathways, certain effects are unique to specific metals. For instance, Pb and Cd induce Blood-Brain Barrier (BBB) disruption, whereas As and Mn are associated with neuroinflammation, glutamate excitotoxicity, impaired Amyloid Precursor Protein processing, aberrant Nitric Oxide (NO) signaling, and cortical and synaptic dysfunction. Our reivew provides a deeper understanding of biological mechanisms showing how metals contribute to AD. Information regarding the potential metal-induced neurotoxicity regarding AD may help us develop effective therapeutic AD intervention and treatment.

Keywords: Alzheimer's disease; neurodegenerative diseases; heavy metals; arsenic; cadmium; mechanistic studies

1. Introduction

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative diseases across the world (Islam et al., 2022; Rahman et al., 2021). About 50 million individuals worldwide suffer from AD or AD-related dementia, which both serious global health concern and one of the most common types of dementia (Alzheimer's Association, 2016; Guo et al., 2020). It has been projected that the prevalence of AD will dramatically increase due to rising life expectancy worldwide. As the

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degeneration of neuron takes place, AD gradually impairs cognitive abilities, including memory, attention, language, judgment and thinking (DeTure and Dickson, 2019). In the advanced stages of AD, patients experience significant memory loss, confusion, hallucinations, and a lack of self-sufficiency. Eventually, AD patients die from respiratory syndrome, infection, or starvation (Guo et al., 2020). Additionally, AD is the most common form of dementia among older adults (Tyczyńska et al., 2024). The increase of AD and Alzheimer's disease related dementia (ADRD) to an estimated 152 million people by 2050 will put remarkable pressure on healthcare systems (GBD 2019 Dementia Forecasting Collaborators, 2022; Li et al., 2022). The initial stage of AD is characterized by the aggregation of amyloid β-protein (Aβ) in senile plaques, the formation of neurofibrillary tangles composed of abnormally phosphorylated tau protein, and a reduction in neuronal cell number, all contributing to declining cognition (Rostagno, 2022; Tyczyńska et al., 2024). Currently, four genes are known to contribute to the development of AD: (i) the amyloid precursor protein (APP), (ii) presenilin 1 (PSEN1), (iii) presenilin 2 (PSEN2) and (iv) the apolipoprotein E (APOE) gene (Blacker, and Tanzi, 1998; Lanoiselée et al., 2017).

The typical onset of sporadic or late-onset AD may be associated with several environmental, lifestyle, and genetic risk factors and thus considered as a multifactorial disorder (Arora et al., 2023; Bellenguez et al., 2022; Bird, 2008; Lau et al., 2023; Rahman et al., 2020; Xia et al., 2018). The most studied mechanisms of the AD pathogenesis are Aβ protein and tau-associated mechanisms (Murphy and LeVine, 2010; Medeiros et al., 2011), glial dysfunction (Yu et al., 2024), mitochondrial dysfunction (Ashleigh et al., 2023), oxidative stress (Dhapola et al., 2024; Gella and Durany, 2009), neuroinflammation (Heneka et al., 2015), calcium dysregulation (Joshi et al., 2023; Yu et al., 2009), as well as various lifestyle and environmental factors also associated with AD pathobiology (Arora et al., 2023; Dosunmu et al., 2007; Guo et al., 2020). Although age, genetics, and lifestyle factors have been established as primary risk factors to the onset of AD, growing evidence indicates that environmental exposures, such as toxic metals, may have adverse effects on AD/ADRD pathogenesis (Rahman et al., 2020; Huat et al., 2019; Suresh et al., 2023; Yegambaram et al., 2015).

Among the environmental risk factors for AD and dementia, air pollution including exposure to ozone, heavy metals, pesticides, Bisphenol A, and microplastics are the most prominent risk factors (Suresh et al., 2023). These factors may be associated with oxidative stress or inflammation as well as numerous genetic and environmental risk factors intersect with the etiology of AD and therefore, illustrating the complexity of the illness (Sheppard and Coleman, 2020). Experts have proposed multiple mechanisms to elucidate the complexity of AD. For instance, Henderson et al. (1988) proposed two hypotheses based on epidemiological data. The first hypothesis suggests that toxic or pathogenic particles aggregate in brain and may induce AD over time. The second hypothesis suggests that environmental exposure, genetic susceptibility, and/or age-related changes of a biological process are essential for cerebral/neuronal dysfunction contributing to AD (Henderson et al., 1988; Suresh et al., 2023). Environmental exposure to metals may induce AD or dementia through one of the two mechanisms highlighted in the above-mentioned hypotheses.

Environmental toxicants, especially heavy metals including arsenic (As), manganese (Mn), lead (Pb), and cadmium (Cd), are widespread pollutants that accumulate in various ecosystems due to human activities such as industrialization, mining, agricultural practices, and urbanization (Angon et al., 2024; Tchounwou et al., 2012). Studies have found that environmental exposure to heavy metals may induce neurotoxicity and possibly influencing the onset of neurodegenerative disorders such as AD and Parkinson's disease (PD) (Bakulski et al., 2020; Chin-Chan et al., 2015; Ijomone et al., 2020; Islam et al., 2022). Prospective associations between neurodegenerative disease (i.e., AD) and elevated exposure to specific metals (such as As, Mn, Pb and Cd) have been found through epidemiological and experimental investigations (Bakulski et al., 2020; Horton et al., 2019; Min and Min, 2016; Spitznagel et al., 2023; Tripathi et al., 2022; Wang et al., 2021; Zhang et al., 2021; Zhou et al., 2018). For example, a population-based cross-sectional study demonstrated that prolonged As exposure may adversely affect adults' cognitive performance in a dose-dependent manner (Wang et al., 2021). Likewise, Mn, a necessary trace element, has shown neurotoxic effects at high

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concentrations that may cause damage to dopaminergic neurons and cognitive impairment leading to AD development (Peres et al., 2016; Martin et al., 2008; Martins et al., 2019). A study was conducted among Chinese elders by Tong et al. and revealed that Mn levels were shown to be markedly elevated in the brains of AD patients with dementia in comparison to healthy individuals and suggested that high Mn levels may have a role in the progression of AD as a critical pathogenic factor (Tong et al., 2014). Prolong Pb exposure, historically linked to cognitive deficit in children (Canfield et al., 2005; Neuwirth et al., 2020), and exposure to Pb during childhood has also been associated with an increased risk of developing neurodegenerative disorders, including AD in adults (Reuben, 2018; Sanders et al., 2009). In the context of neurodegeneration, Cd exposure is involved in calcium signaling disruption (Jiang et al., 2015), inducing oxidative stress (Branca et al., 2020), and causing mitochondrial dysfunction (Li et al., 2024) which are intricately associated with AD pathology (Ali et al., 2021; Arruebarrena et al., 2023). A population-based study conducted by Peng and colleagues demonstrated that there is a positive relationship between Cd exposure and mortality from AD (Peng et al., 2017). Similarly, another epidemiological study showed a significant association between blood Cd levels and AD mortality among older adults in the US (Min and Min, 2016).

Despite over century since AD was first identified by German psychiatrist and neuropathologist Dr. Alois Alzheimer in 1906, intricate molecular pathways underlying the pathophysiology of AD remain inadequately understood (Hippius and Neundörfer, 2003; Rostagno, 2022). In particular, the development of AD induced by metal exposures primarily due to As, Mn, Pb and Cd and the underlying mechanisms are yet to be fully understood. Notably, most published reviews have focused on single metal exposure rather than providing comprehensive insights and thorough comparisons of the mechanisms that illustrate the pathways of the development of AD/ADRD (Brown et al., 2019; Chib and Singh, 2022; Chin-Chan et al., 2019; Gong and O' Bryant, 2010; Rahman et al., 2021). Therefore, the aim of this review is to summarize contemporary mechanistic research exploring the links between multiple metals such as As, Mn, Pb, and Cd, exposures and their contribution in AD development using data from the most recent mechanistic studies, i.e., studies conducted in the past 10 years. Through the review of the recent data, we seek to pinpoint common routes, processes and molecular mechanisms by which these metals could affect and/or contribute to the development and onset of AD.

2. Methods

2.1. Search Strategy

Relevant primary research articles, published from 2014 through 2024, were identified using the PubMed Database. The literature search was conducted during August-September 2024 to collect information on the associations of As, Mn, Pb and Cd with Alzheimer's Disease (AD). We restricted our searches to studies published in peer-reviewed English-language journals, within the last 10 years. The following keywords were used: Arsenic AND Alzheimer's Disease; Cadmium AND Alzheimer's Disease; Manganese AND Alzheimer's Disease; and ("Lead"[Mesh]) AND "Alzheimer Disease"[Mesh]. A total of 391 articles were retrieved and screened using the following inclusion and exclusion criteria (Figures 1 and 2). Selected articles were then retrieved for full-text screening and data extraction.

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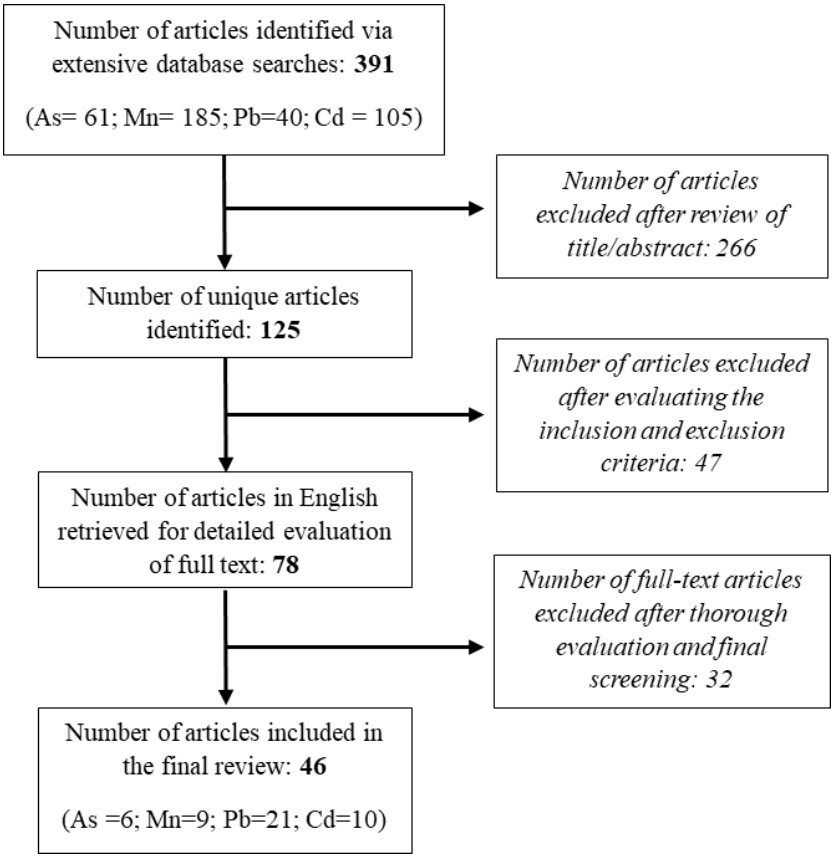

Figure 1. The study selection process.

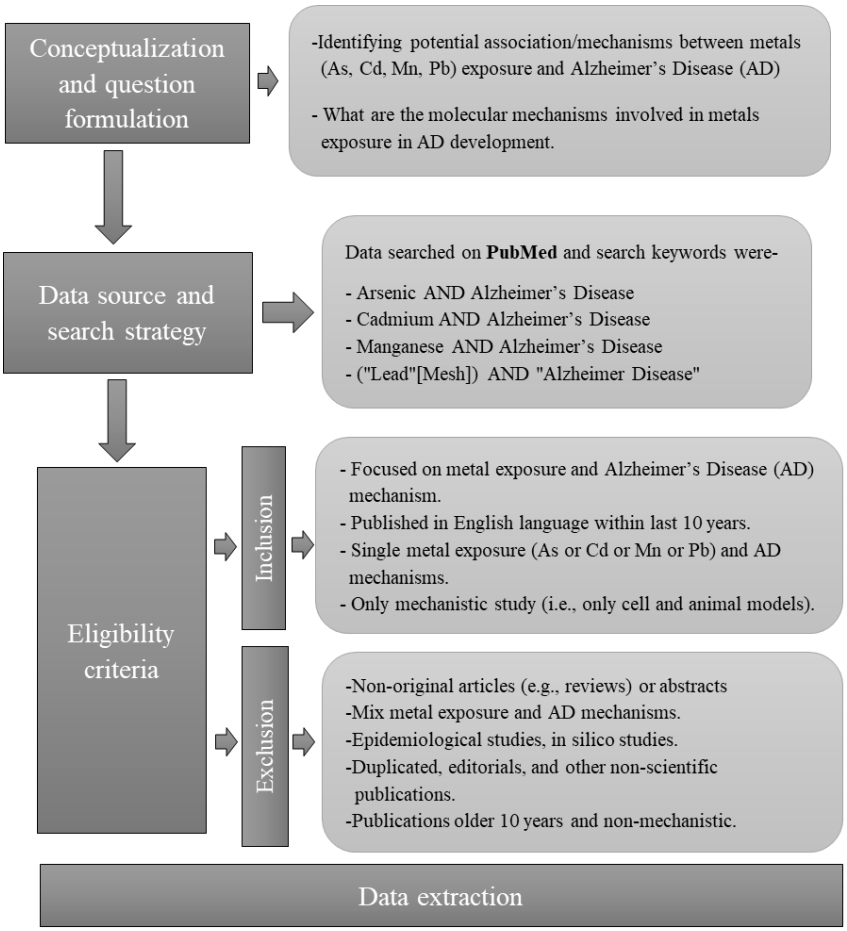

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Figure 2. Details of data source, search strategy and eligibility criteria.

2.2. Inclusion Criteria

Studies were included if (1) focused on metal exposure and Alzheimer's Disease (AD) mechanisms, (2) were published in English language within the last 10 years, (3) investigated single metal exposure (As or Cd or Mn or Pb) and AD mechanisms, (4) were only mechanistic study (i.e., only cell and animal models) (Figure 2).

2.3. Exclusion Criterion

Studies were excluded if they (1) did not focus on AD, (2) were non-original articles (e.g., reviews) or abstracts, (3) investigated mix metal exposure and AD mechanisms, (4) were epidemiological studies, in silico studies, (5) were duplicated, editorials, and other non-scientific publications, (6) were older than 10 years or non-mechanistic (Figure 2).

2.4. Data Extraction

The following predetermined variables were extracted from the selected articles (n=46): (1) Bibliographical data (authors name, year of publication), (2) Title, (3) Objective of the study, (4) Design of the study, (5) Exposure, (6) Outcomes, (6) Key findings of the study. A total of 125 unique studies were identified. After reviewing abstracts, full-text articles and their reference sections, 46 articles were finally selected for further analysis for this review (Figure 1).

3. Results

After an extensive literature search and final screening, a total of 46 original research articles were selected for this review. Among the 46 articles, 6 are related to As exposure, 9 to Mn exposure, 21 to Pb exposure and 10 to Cd exposure and AD pathobiology. The results of the selected studies are presented in Tables 1-4.

3.1. Mechanisms and Pathobiology of AD Development Related to Arsenic Exposure

Arsenic (As) is one of the well-known naturally occurring toxic metalloid prevalent in the Earth's crust. Drinking water and As-contaminated foods are the primary sources of human exposure to environmental As (Rahaman et al., 2021; 2022). Although the molecular mechanism of As-associated pathobiology in AD remain unclear, experimental research and epidemiological data indicate that As produces neurotoxicity and affects memory and cognition, which are the symptoms of the AD patients (Rahman et al., 2021; Tyler and Allan, 2014). Exposure to environmental As and its metabolites triggers several pathogenic events, including oxidative damage, inflammation, mitochondrial dysfunction, ER stress, apoptosis, compromised protein homeostasis, and aberrant calcium signaling. Research has shown that these changes align with the majority of AD's pathological, biochemical, and clinical manifestations (Rahman et al., 2021).

The review provides updated mechanistic insights into the impact of arsenic exposure on Alzheimer's disease (AD) development and pathology, based on six recent studies. Of these, three were conducted using mice model (Tripathi et al., 2022; Pakzad et al., 2021; Niño et al., 2018a), two were conducted on Rats (Niño et al., 2021; Niño et al., 2018b) and one study was carried out using SH-SY5Y Cells (Wisessaowapak et al, 2021). The key findings from these mechanistic studies are grouped into three thematic categories, which are discussed below and summarized in Table 1.

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Table 1. Literature summary of the mechanistic studies for Arsenic exposure and AD pathobiology.

SL	References	Study objective	Study type	Exposure	Outcomes	Key Findings
1	Tripathi et al., 2022	Investigated nitric oxide signaling in arsenic neurotoxicity using mice model.	Mice model	Mice-drinking water	AD and ASD	Low doses arsenic exposure disrupts the S-nitrosylation (SNO) signaling in the striatum and hippocampus, affecting key proteins, mitochondrial respiratory function, endogenous antioxidant systems, transcriptional regulation, cytoskeleton maintenance, and regulation of apoptosis. This disruption leads to impaired neurodevelopment, neuronal function, and cell viability, resembling features of ASD and AD pathobiology.
2	Niño et al., 2021	Investigated synaptic structure (cortical microstructure and synapses) in chronic arsenic exposure using both a triple-transgenic Alzheimer's disease model and Wistar rats.	Triple-transgenic Alzheimer's disease model and Wistar rats	Rats-drinking water	Cognitive impairment (AD)	Chronic arsenic exposure alters cortical microstructure and synaptic connectivity as indicated by high ADC and low FA, suggesting structural reorganization. Dendritic spine density increased at 2 months but decreased at 4 months. Synaptophysin levels increased at 2 months, remained stable at 4 months while PSD-95 protein levels decreased in arsenic-exposed groups at 4 months suggesting arsenic affects development and stabilization of dendritic complexity.
3	Wisessaowapak et al, 2021	Investigated and determined whether prolonged exposure to arsenic affected the phosphorylation of wild-type tau in the neuronal cell model (SH-SY5Y Cells).	SH-SY5Y Cells	Cells	AD	Prolonged arsenic exposure increases tau phosphorylation in neurons, reducing dephosphorylated tau and elevates pS202 tau and GSK3β activity, leading to tau hyperphosphorylation. This enhances insoluble tau aggregation in cells, suggesting a link to sporadic Alzheimer's disease.
4	Pakzad et al., 2021	Investigated the correlation between arsenic trioxide exposure and its impact on the tau protein Ser262 phosphorylation after 3 months of exposure via drinking water in male mice.	Mice model	Mice-drinking water	AD	Arsenic accumulation in the brain, likely due to the BBB integrity disruption. Tau phosphorylation at Ser262 increased significantly after 3 months of exposure to 10 ppm arsenic. Low arsenic levels may raise the risk of neurodegenerative disease.
5	Niño et al., 2018a	Investigated arsenic exposure and the pathophysiological progress of AD using the 3xTgAD mouse model.	3xTgAD mouse model	Mice-drinking water	AD	Chronic arsenic exposure exacerbates AD-like pathology in mice potentially triggering neurodegeneration through mitochondrial dysfunction, leading to behavioral deficits, cognitive decline, sleep disturbances, altered circadian rhythm and locomotor activity. Exposed mice also exhibited elevated level of amyloid and tau

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							along with oxidative stress and energy deficits in the hippocampus. Early life exposure poses major risks for cognitive decline.
6	Niño et al., 2018b	Investigated the effects of chronic arsenic exposure on the production and elimination of Amyloid-β (Aβ) in Wistar rats.	Male rats	Wistar	Rats-drinking water	AD	Chronic arsenic exposure leads to cognitive deficits in rats, increasing Aβ (1–42) production, BACE1 enzymatic activity and elevating receptor for advanced glycation end products (RAGE) levels (approximately 220-fold). Behavioral deficits observed in in fear conditioning test. No changes in LRP1 expression were noted with arsenic exposure. Arsenic exposure disrupts amyloid clearance equilibrium in the brain, supporting it's role in neurodegenerative disease development.

3.1.1. Insights from Mouse Models of Arsenic Exposure

Arsenic and Bioenergetic Dysfunction in Alzheimer's Disease

Bioenergetic dysfunction is a hallmark in Alzhemer's disease (AD) and play crucial role in its pathogenesis. Employing the 3xTg-AD mouse, a well-established and widely used model for AD, Nino et al., demonstrated that chronic arsenic exposure (3 ppm) from gestation to 6 months disrupts mitochondrial bioenergetics. Mitochondria isolated from the hippocampus of these mice exhibit reduced ATP production, impaired respiratory chain activity, and increased reactive oxygen species (ROS) generation. Immunohistochemical analysis further showed increased amyloid plaques and tau phosphorylation, two characteristic features of AD pathology. Behavioral studies revealed spatial memory deficits and disruption of circadian rhythms, indicating that arsenic accelerates neurodegenerative processes through mitochondrial dysfunction and exacerbating oxidative stress, both of which are central to AD pathology (Niño et al., 2018a).

Arsenic and Tau Phosphorylation: A Key Marker of AD

The increase level of hyperphosphorylated tau is another common feature of Alzheimer's disease. Using male mice, Pakzad et al. explored the effects of different dosages (1 and 10 ppm) of arsenic trioxide exposure on tau protein phosphorylation, specifically at the Ser262 site, which plays a critical role in tauopathies. The researchers found that after three months of exposure to arsenic at 10 ppm, significant increases in tau phosphorylation at Ser262 were observed. Interestingly, low-dose exposure (1 ppm) did not cause significant changes, suggesting a dose-dependent effect of arsenic on tau hyperphosphorylation. The increased tau phosphorylation observed in the high-exposure group parallels key features of AD and tauopathies, reinforcing the idea that arsenic exposure could contribute to the risk of developing neurodegenerative disorders through tau-related mechanisms (Pakzad et al., 2021).

Arsenic-Induced Nitric Oxide Dysregulation and Neurotoxicity

Beyond mitochondrial dysfunction and tau pathology, another critical signaling pathway affected by arsenic is nitric oxide (NO) signaling. Nitric oxide is involved in a variety of cellular processes, including the regulation of mitochondrial function and apoptosis. In an elegant study, Tripathi et al. revealed that arsenic-exposed mice exhibited significant alterations in S-nitrosylation (SNO) signaling pathways, which regulate mitochondrial respiration, antioxidant defense, and apoptosis. These mice also displayed cognitive dysfunctions similar to those observed in autism spectrum disorder (ASD) and AD models. Furthermore, SNO-enrichment analysis revealed

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disrupted processes involving mitochondrial function, cytoskeleton maintenance, and transcriptional regulation, all of which are critical for neuronal health and survival. These findings underscore the potential role of NO and SNO signaling in arsenic-mediated neurotoxicity and highlight the convergence of arsenic exposure effects with the genetic mutations associated with ASD and AD (Tripathi et al., 2022).

3.1.2. Findings from Rat Models of Arsenic Exposure

Neurotoxicity and Amyloid-β Production, Synaptic and Cortical Changes

Chronic arsenic exposure is increasingly recognized as a potential environmental risk factor for neurodegenerative diseases such as AD. Several studies have investigated its impact on various cellular and molecular processes associated with neurodegeneration. One study by Niño et al. (2018) investigated the effects of arsenic exposure on amyloid-β (Aβ) production and clearance in Wistar rats. Rats were exposed to 3 ppm of arsenic from gestation to four months of age, resulting in behavioral deficits and a marked increase in cleaved Aβ(1–42) levels in brain lysates, a key pathological feature of AD. This was accompanied by elevated receptor for advanced glycation end products (RAGE) and increased β-secretase (BACE1) activity, suggesting that arsenic exposure may disrupt Aβ processing and contribute to amyloid accumulation in the brain (Niño et al., 2018b).

Building on these findings, a separate study by Niño et al. (2021) examined the effects of chronic arsenic exposure on cortical synaptic connectivity and structure in both Wistar rats and a triple-transgenic AD mouse model. Chronic exposure to 3 ppm sodium arsenite from gestation through postnatal development led to changes in cortical microstructure, as indicated by diffusion-weighted imaging showing altered apparent diffusion coefficient (ADC) and fractional anisotropy (FA) values. Furthermore, the analysis of synaptic markers revealed decreased synaptic connectivity, with abnormal dendritic spine morphology and increased spine density observed at younger ages. These structural changes in the cortex and synaptic regions may underlie the cognitive impairments seen with arsenic exposure and could potentially progress to neurodegeneration in older animals (Niño et al., 2021).

3.1.3. Mechanistic Insights from Cell Line: Tau Hyperphosphorylation and Aggregation

In a recent study, Wisessaowapak et al. (2021) explored the effects of long arsenic exposure on tau phosphorylation in differentiated SH-SY5Y neuroblastoma cells, which may contribute to Alzheimer's disease (AD) pathogenesis. They showed that low micromolar concentrations of sodium arsenite increased tau phosphorylation at specific residues (pS202), while decreasing dephosphorylated tau (Tau 1). Arsenic exposure activated two key kinases: GSK3β and ERK1/2. Inhibition of these kinases using specific inhibitors (BIO, SB216763, lithium, and U0126) reversed the effects of arsenic on tau phosphorylation. Additionally, arsenic exposure increased tau aggregation and promoted the redistribution of tau from the membrane fraction to the cytosol, where neurofibrillary tangles may form. This study suggests that arsenic-induced tau hyperphosphorylation, mediated by GSK3β and ERK1/2 activation, could contribute to the development of sporadic AD (Wisessaowapak et al., 2021).

Collectively, the recent mechanistic studies mentioned above revealed the deleterious impact of arsenic exposure on the biological processes of the nervous system, leading to cognitive impairments resembling those observed in AD.

3.2. Mechanisms and Pathobiology of AD Development Related to Manganese Exposure

Manganese (Mn) is one of the essential trace metals primarily obtained through dietary sources. It plays a vital role in enzyme function, bone formation, carbohydrate metabolism, and antioxidant activity. While Mn is necessary in trace amounts, inhaling high concentrations of the metal can cause Mn buildup in the brain and manganism, an illness that resembles parkinsonian disease. Mn accumulation can be occurred in the brain through dietary intake as it crosses the Blood Brain Barrier

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(BBB) as well as through inhaled manganese, absorbed by the olfactory transport system. Animal studies have established that excessive Mn exposure can cause oxidative stress, impaired MnSOD activity, and contribute to AD pathology including Aβ accumulation and tau phosphorylation (Bakulski et al., 2020; Rizor et al., 2021). Manganism is a unique neurological disease linked to extremely high manganese exposure. The effect of Mn exposure on the nervous system are influenced by the levels of other essential metals.

In this review, we summarized findings from nine mechanistic studies that highlight the pathobiology and disease development of AD related to Mn exposure. Five of these studies examined the pathobiology of AD using cell lines (Xu et al., 2021; Rizor et al., 2021; Pajarillo et al., 2020; Lu et al., 2018; Kirkley et al., 2017), while the remaining four studies investigated the disease mechanism using both mouse models and cell lines exposed to Mn (Fan et al. 2024; Spitznagel et al., 2023; Pajarillo et al., 2022; Yang et al., 2021). The key findings and details of the nine mechanistic studies related to Mn exposure in AD development mechanisms are discussed below and summarized in Table 2.

Table 2. Literature summary of the mechanistic studies for Manganese exposure and AD pathobiology.

SL	References	Study objective	Study type	Exposure	Outcomes	Key Findings
1	Fan et al. 2024	Investigated the role of Drp1 in manganese exposure induced autophagy and mitochondrial function. Determined if Drp1 inhibition improves autophagy independent of mitochondria.	Mechanistic-HeLa cells, N27 neuronal cells and mice	Cells and mice-orally gavage	PD and AD	Manganese exposure impairs autophagy without affecting mitochondria at low concentration. Partial Drp1 inhibition improves autophagy flux independently of mitochondrial function. Drp1 knockdown reduces protein aggregation in neurological disorders. Autophagy pathways are dysregulated in mouse models treated with manganese. Drp1 inhibition protects against manganese-induced autophagic impairment. This study highlights autophagy as a target of low manganese exposure.
2	Spitznagel et al., 2023	Investigated acute Mn exposure effects on glutamatergic neurotransmission, evaluated glutamate clearance dynamics in astrocytes post-Mn exposure, investigated behavioral consequences of Mn exposure in AD models and identified vulnerabilities to Mn exposure in pre-symptomatic AD phases.	Mice and Primary astrocytes	Mice and Primary Astrocytes-Drinking water	AD	Manganese exposure altered glutamate clearance in astrocytes, increased cortical GLAST expression, and increases seizure susceptibility in APP/PSEN1 mice. No changes were observed in hippocampal long-term potentiation after manganese exposure. Acute manganese exposure lead to glutamatergic dyshomeostasis which may contribute to early Alzheimer's disease pathogenesis.
3	Pajarillo et al., 2022	Investigated the effects of astrocyte-specific deletion of REST in the striatum of Mn-exposed mice to test if astrocytic REST modulates Mn toxicity. In short, it investigated astrocytic REST's role in Mn-induced neurotoxicity, assessed locomotor and cognitive function impairment, and evaluated the impact of astrocytic REST deletion on proinflammatory factors.	Mice and Primary astrocytes	Mice and Primary Astrocytes-Nostril	PD, AD	Astrocytic REST deletion in the striatum of the mouse brain exacerbated Mn-induced toxicity, including nigrostriatal dopaminergic dysfunctions, motor deficits, and cognitive impairment, along with molecular changes in inflammation and glutamate transporter GLT-1. Astrocytic REST deletion worsened manganese-induced neurotoxicity in mice.

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4	Xu et al., 2021	Investigated Mn-induced autophagy dysfunction in N2a cells, explored the role of PP2Ac methylation in autophagy regulation, evaluated the effects of ABL-127 on PP2Ac methylation and assessed the impact of LCMT1 overexpression on autophagy.	N2a cells	N2a cells	PD, AD	This study demonstrated that autophagy disruption is related to cytotoxicity caused by Mn in N2a cells. mTORC1/ULK1 activation and PP2Ac demethylation contribute to autophagy modulation, and methylated PP2Ac can ameliorate autophagy dysfunction by inactivating mTORC1/ULK1 and reducing oxidation. It also suggests that the regulation of PP2Ac methylation is a promising research direction for the prevention and treatment of Mn neurotoxicity and even neurodegenerative diseases.
5	Rizor et al., 2021	Investigated Mn-induced YY1 activation via the NF-kB pathway and examined mechanisms impairing EAAT2 function in astrocytes.	H4 human astrocyte cells	Cells	PD, AD	Results demonstrate that Mn exposure induced oxidative stress and TNF-α production, leading to the canonical phosphorylation of the upstream kinase IKK-β, increased YY1 promoter activity and mRNA/protein levels, and consequent EAAT2 repression. Mn exposure activates IκB kinase, impairing EAAT2 function. The NF-κB signaling pathway mediates YY1 activation by Mn. Oxidative stress and TNF-α are upstream of IKK-β activation.
6	Yang et al., 2021	Investigated Mn-induced cognitive impairment mechanisms by assessing the role of APP in cognitive deficits, evaluating APP's secretase processing in neurotoxicity, exploring synaptic dysfunction by using both in vivo mouse model and in vitro cell culture (N2a cells).	astrocyte cell	Mice and N2a cells-gastric gavage	AD	Manganese exposure impairs cognition in mouse models, inhibits APP expression and α-secretase activity. No effect on β-secretase levels or activity was observed. Mn-induced cognitive impairment is related to synaptic dysfunction. The findings suggest similarities to early Alzheimer's disease mechanisms. Dysregulated APP processing contributes to cognitive deficits caused by manganese. s
7	Pajarillo et al., 2020	Investigated the role of RE1-silencing transcription factor (REST) in dopaminergic neurons against Mn-induced toxicity and exmined the enhancement of the expression of the dopamine-synthesizing enzyme tyros ine hydroxylase (TH)	Neuronal cell lines (Mouse CAD cell line and LUHMES (CRL-2927) cell line)	Cells	PD, AD	The findings indicated that REST upregulates tyrosine hydroxylase (TH) expression in dopaminergic neurons and protects neurons from manganese (Mn)-induced toxicity by reducing oxidative stress and inflammation, inhibiting proapoptotic proteins, nhancing antiapoptotic proteins and promoting the expression of antioxidant proteins like catalase and Nrf2. REST also binds to RE1 sites in the TH promoter. Therefore, REST's dysfunction is linked to Parkinson's and Alzheimer's diseases. Finally, it was revealed that REST activates TH expression and thereby protects neurons against Mn-induced toxicity and neurological disorders associated with dopaminergic neurodegeneration.
8	Lu et al., 2018	Investigated the function of the gap junctional intercellular	Mechanastic-primary astrocytes	Primary astrocytes	Neurotoxicity, PD, AD	This research contributes to understanding how manganese exposure affects astrocyte

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		communication (GJIC) in apoptosis induced by Mn by examining the Cx43 expression during excessive manganese exposure, excitotoxicity cell death mechanisms and glutamate homeostasis disruption due to manganese exposure.				communication and glutamate regulation, which could have implications for various neurological disorders associated with glutamate excitotoxicity. Manganese exposure significantly reduced astrocyte viability, increased apoptosis, disrupted glutamate homeostasis in astrocytes, elevated intracellular glutamate levels, Glutamate transporter expression was downregulated.
9	Kirkley et al., 2017	Investigated the role of microglia and glial crosstalk in Mn-induced neurodegeneration.	Mechanastic-Mixed glial cultures from whole brain (astrocytes and microglia)	Cells	Neurotoxicity, AD, PD, Dementia	This study demonstrated that Mn is a potent inducer of an inflammatory phenotype in microglia that is essential for the activation of astrocytes, suggesting there are critical signaling pathways in glial cells for neuroinflammatory injury from Mn. It also revealed that the NF-κB signaling in microglia plays an essential role in inflammatory responses to Mn toxicity by regulating cytokines and chemokines that amplify the activation of astrocytes.

3.2.1. Cell line and Manganese Exposure

Drp1 Role in Neuroprotection and Mn-Induced Toxicity

Dynamin-related protein 1 (Drp1) is crucial for mitochondrial dynamics and fission. Partial inhibition of Drp1 is protective in neurodegenerative disorders like Parkinson's (PD) and Alzheimer's (AD), primarily by improving mitochondrial function. However, studies reveal that Drp1 inhibition also reduces protein aggregation, implicating autophagy. Dose-response studies in HeLa and N27 rat immortalized dopamine neurons showed that Mn impairs autophagy flux without affecting mitochondrial function. Autophagy dysregulation was observed in dopamine neurons, but not in GABA neurons of low Mn-treated mouse. Drp1 knockdown or partial inhibition mitigated Mn-induced autophagy impairment and reduced α-synuclein aggregation, suggesting Drp1's protective effects extend beyond mitochondrial fission. Drp1 inhibition improves autophagy flux, independent of its mitochondrial role, offering potential therapeutic insights for neurodegenerative diseases linked to autophagy impairment (Fan et al, 2024).

Impact of Mn Exposure on Autophagy

Using the mouse N2a blastoma cell line, Xu et al. revealed that Mn levels above 500 μmol/L caused cell damage and oxidative stress by downregulating PP2Ac methylation, a key regulator of autophagy. This led to mTORC1 activation and autophagy dysfunction. Interventions with the PPME-1 inhibitor ABL-127 and LCMT1 overexpression restored PP2Ac methylation, ameliorating autophagy dysfunction, oxidative stress, and cytotoxicity, suggesting that enhancing PP2Ac methylation offers a protective strategy against Mn-induced neurotoxicity (Xu et al., 2021).

Mn exposure Impairs Astrocytic Glutamate Transporter, EAAT2

Chronic manganese (Mn) exposure impairs the astrocytic glutamate transporter EAAT2, contributing to neurodegenerative diseases like Parkinson's and Alzheimer's. Rizor et al. showed that when the H4 human astrocyte cell line is exposed to pathologically relevant concentrations of Mn (250 μM), it induces oxidative stress and TNF-α production, leading to the activation of the IKK-β

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kinase. This triggers NF-κB p65 translocation, increasing transcription factor Ying Yang (YY1) levels and repressing EAAT2 (Rizor et al., 2021).

REST Protects Dopaminergic Neurons Against Manganese-Induced Neurotoxicity

Chronic Mn exposure causes dopaminergic dysfunction and neurodegeneration that result in disorders like manganism and AD. In a recent study, Pajarillo et al., demonstrated that the transcription factor REST represses Mn-induced toxicity in dopaminergic neurons through a concurrent induction of the expression of tyrosine hydroxylase, the enzyme that catalyzes dopamine synthesis. REST binds to the promoter of TH, recruits the epigenetic modifiers CBP/p300, and thereby increases TH transcription, mRNA, and protein. Moreover, REST reduced Mn-induced oxidative stress, inflammation, and apoptosis by reducing TNF-α, IL-1β, IL-6, IFN-γ, the proapoptotic proteins Bax and Daxx, while promoting antioxidant proteins such as catalase, Nrf2, and HO-1. These results pointed to the potential therapeutic role of REST in treatment against Mn-induced dopaminergic neurodegeneration (Pajarillo et al., 2020).

Glutamate Excitotoxicity in Mn-Induced Neurotoxicity

Excessive glutamate stress is implicated in conditions like cerebral ischemia, brain trauma, and neurodegenerative diseases such as PD and AD. Disruption of glutamate homeostasis is central to manganese (Mn) neurotoxicity. Astrocytes, which maintain glutamate balance and constitute ~50% of CNS neuronal cells, are highly sensitive to Mn-induced toxicity. Their gap junctions (GJ), primarily formed by connexin43 (Cx43), mediate intercellular communication of small molecules like glutamate. In experiments with cultured astrocytes exposed to Mn (0–1000 μM), Lu et al., recently revealed that Mn exposure reduces astrocyte viability, increases apoptosis, and elevates intracellular and extracellular glutamate levels in a dose-dependent manner. Additionally, Mn impairs gap junction intercellular communication (GJIC) by reducing connexin43 (Cx43) expression and inhibiting gap junction function, disrupting the transfer of signaling molecules like glutamate. These findings suggest that Mn-induced glutamate excitotoxicity is driven by GJ dysfunction and reduced Cx43 expression (Lu et al., 2018).

Role of Mn Exposure and NF-κB in Neuroinflammation

Microglia are the immune cells of the central nervous system (CNS). They become activated in response to injury, infection, or neurological diseases, including Alzheimer's disease (AD), often serving as an early indicator of neurological distress—a process known as microgliosis. Microgliosis is often followed by astrogliosis—reactive responses of astrocytes (another type of glial cell)—both of which contribute to neuroinflammation and exacerbate neuronal damage. While both microgliosis and astrogliosis occur in Alzheimer's disease and manganese-induced neurotoxicity, how these glial populations interact with each other is still poorly understood. Kirkly et al. showed that Mn exposure caused dose-dependent increases in pro-inflammatory gene expression and morphological changes in microglia, leading to the release of cytokines and chemokines. Conditioned media from Mn-activated microglia amplified inflammatory responses in astrocytes by increasing mRNA levels of Tnf, IL-1β, IL-6, Ccl2, and Ccl5. Blocking NF-κB inhibited astrocyte activation, while TNF knockdown partially reduced inflammation, highlighting TNF's role in microglia-astrocyte crosstalk. The findings underscore NF-κB as a key regulator of neuroinflammation and a potential target for reducing astrocytic inflammatory responses and neurodegeneration (Kirkly et al., 2017).

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3.2.2. Mouse Model and/or cell Line Manganese Treatment

Manganese-Induced Toxicity Impairs Glutamatergic Signaling

Manganese (Mn) induced neurotoxicity and Alzheimer's disease (AD) exhibit dysregulated glutamatergic signaling. Mn toxicity may impair glutamate clearance, disrupt glutamatergic homeostasis, and increase susceptibility to seizures. Indeed, in a recent study, using APP/PSEN1 and wild-type mice, researchers combined in vitro and in vivo approaches to assess astrocytic glutamate clearance and behavioral outcomes following acute Mn exposure. Results show that even limited Mn exposure accumulates in brain tissue, disrupts glutamate clearance in cortical astrocytes, and heightens seizure susceptibility without affecting hippocampal long-term potentiation (LTP). These effects occur in young adult mice before significant AD-related pathology, suggesting glutamate dysregulation as an early AD feature and Mn exposure as a potential amplifier of genetic risk (Spitznagel et al., 2023).

Astrocytic REST (Repressor Element-1 Silencing Transcription Factor) Role in Mn-Induced Neurotoxicity

Manganese (Mn) accumulates in the brain, especially in brain regions such as the striatum and globus pallidus, through disturbing mitochondrial function, oxidative stress, inflammation, and excitotoxicity—common neurodegenerative pathways observed in Alzheimer's disease and Parkinson's disease. REST, a zinc-finger transcription factor, regulates neuronal and astrocytic gene expression, including glutamate transporters like EAAT2, which protect neurons from excitotoxicity. While neuronal REST's protective role in AD and PD is well-documented, the role of astrocytic REST remains underexplored. Studies show that astrocytic REST deletion exacerbates PD-related dopaminergic neuronal loss and increases inflammation. In Mn-exposed mice, REST deletion in the striatum led to worsened dopaminergic dysfunction, motor deficits, cognitive impairments, inflammation, and reduced glutamate transporter GLT-1. These findings highlight REST's critical role in mitigating Mn-induced neurotoxicity and glutamate dysregulation, emphasizing astrocytic REST as a potential therapeutic target for Mn-related neurodegeneration and broader neurodegenerative disorders. The striatum was chosen for this study due to its vulnerability to Mn accumulation, excitotoxic lesions, and dopaminergic degeneration, providing insights into region-specific astrocytic REST functions (Pajarillo et al., 2022).

Mn-Induced Dysregulation Amyloid Precursor Protein (APP) Processing and Cognitive Impairment

Excessive manganese (Mn) exposure causes cognitive deficits similar to Alzheimer's disease (AD) by affecting amyloid precursor protein (APP) and its processing. APP, critical in AD pathology, undergoes cleavage by α- and β-secretases, influencing synaptic function. In Mn-exposed mice and Neuro-2a cells, APP, α-secretase (ADAM10), and soluble APP alpha (sAPPα) levels decreased, along with synaptic protein expression and α-secretase activity. However, β-secretase, Aβ peptides, and β-secretase activity were unaffected. Mn exposure alters non-amyloidogenic APP processing, impairing cognition and synaptic function, linking APP dysregulation to cognitive decline (Yang et al. 2021).

3.3. Mechanisms and Pathobiology of AD Development Related to Lead Exposure

Lead (Pb) exposure-related toxicity was mentioned surprisingly as early as in 370 BC with major sources including old plumbing, paints in the old house, industrial applications, Pb smelters, waste incinerators, automobile Pb-acid batteries (Bakulski et al., 2020). Approximately 1% of global disease burden is associated with Pd exposure, which also has lasting effects on behavioral issues and children's IQ (WHO, 2010; Grandjean, and Bellanger, 2017). Although Pb exposure is particularly more devastating on child health and development, it also contributes to various disease

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development in older adults including amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), hearing loss, age-related cataracts, glaucoma, and other chronic conditions (Bakulski et al., 2020). Environmental Pb exposure can occur through ingestion, inhalation and endogenous sources, with the majority of exposure happening via inhalation or ingestion. Once in the body, Pb is absorbed into cells and tissues, circulating in the bloodstream. Pb can cross both the placental and blood-brain-barrier (BBB), accumulating in the brain due to low excretion rate. Pb, a well-established neurotoxicant, causes oxidative stress by depleting thiols and disrupting the antioxidant defense system. The primary neurotoxic mechanisms of the Pb exposure include excessive oxidative stress, triggering the endoplasmic reticulum stress, mitochondrial disfunction and neuronal cell death it also creates neuroinflammations, excitotoxicity and disruption of the essential metal homeostasis in the brain (Bakulski et al., 2020).

Animal models (i.e., mouse, rats, and zebrafish) treated with lead exhibit the mechanisms and symptoms of AD. While consistent AD-related deficits are documented, the effects of Pb exposure differ by species, timing, dose, and length of exposure. The current review discusses twenty-one mechanistic studies on Pb exposure and AD pathobiology. Among these, seven studies employed different cell lines, ten used mice as models and/or different cell lines, two used zebrafish, and two used rats as a model animal to investigate the link between environmental Pb exposure and AD pathobiology. Table 3 summarizes the main findings of these twenty-one mechanistic investigations.

Table 3. Literature summary of the mechanistic studies for Lead exposure and AD pathobiology.

SL	References	Study objective	Study type	Exposure	Outcomes	Key Findings
1	Rogers et al., 2016	Investigated the effect of Pb on iron homeostasis proteins in human neurons. Study the role of amyloid precursor protein (APP) in maintaining safe intracellular iron levels.	Mechanistic-human neuroblastoma SH-SY5Y cells-*In Vitro*	Cells	neurotoxicity	Acute oxidative stress can result from the reduction of APP translation due to Pb exposure, which is associated to a rise in iron levels in neurons and glia without corresponding ferritin storage. Pb inhibits APP translation, raising cytosolic iron levels. Through the restoration of APP production, iron supplementation protects cells from Pb toxicity. The amyloid precursor protein (APP) is essential for preserving appropriate intracellular iron levels. Pb strengthens the inhibition of APP and FTH translation caused by IRP/IRE. Children with lead poisoning can benefit from iron administration as a treatment.
2	Wang et al., 2022	Investigated how Pb affected microRNAs (miRNAs), post-transcriptional regulators that may be involved in the pathophysiology of AD.	Mechanistic-Mice-animal model	Mice-Drinking water	AD	Modulation of the miR-124-3p/BACE1 pathway plays a crucial role in Pb-induced AD-like amyloidogenic processing. BACE1 is upregulated in the PFC and hippocampal regions after exposure to Pb. miRNAs could be used as stand-in markers to diagnose illnesses. Pb exposure modifies miRNA expression, which impacts brain processes.
3	Bandaru et al., 2022	Investigated the mitophagy marker proteins, including PINK1 and Parkin, in differentiated SH-SY5Y cells to examine the impact of Pd exposure on the PINK1/Parkin dependent pathway.	Mechanistic-SH-SY5Y cells	Cells	AD	Cells treated to Pb, both Aβ (25–35) and Aβ (1–40) separately and in various combinations showed a significant reduction in PINK1 and Parkin levels, which led to defective mitophagy. The Pb-exposed groups showed decreased mitochondrial mass, increased MPTP opening, depolarization of membrane potential, and increased generation of ROS within the mitochondria. By activating the Bak protein, which releases cytochrome c from mitochondria via MPTP and

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						subsequently activates the cytosolic caspase-3 and AIF (apoptosis inducing factor) proteins, Pb may cause apoptosis. The results show that Pb-induced neurotoxicity may be caused by processes such as PINK1/Parkin-mediated mitophagy and defective mitochondria-mediated apoptosis.
4	Eid et al., 2016	Investigated how early life exposure to lead (Pb) can cause epigenetic modifications and late-life changes.	Mechanistic-mice model	Mice-Drinking water	AD	The findings indicate a connection between Pb exposure throughout early life and its potential to reprogram the expression of epigenetic intermediates involved in histone modification or DNA methylation, which in turn control the expression of latent AD-related genes. The latent increases in AD-related proteins in the brain may be mediated by epigenetic modifiers, which are impacted by prenatal exposure to Pb.
5	Xie et al., 2023	Investigated the effects of Pb exposure on AD-like pathogenesis in human cortical neurons.	Mechanistic-human iPSC-derived cortical **neurons** as a model system	human iPSC-derived cortical neurons	AD	The results offer support for the idea that developmental Pb exposure-induced Ca dysregulation is a likely molecular mechanism behind the elevated risk of AD in groups exposed to developmental Pb. Developmental Pb exposure is linked to persistent neuronal alterations and AD hallmarks (elevated tau aggregation and phosphorylation, Aβ42/40). Epigenetic modifications and DNA methylation changes were observed post-Pb exposure. A higher risk of neurological disorders is linked to long-term low-level Pb exposure.
6	vonderEmbse et al., 2017	Investigated the association between early toxicant exposure and systematic microglia activation, possibly reversing the pathological severity of AD.	Mechanistic-mouse model	Mouse-Drinking water	AD	According to this research, early exposure to Pb may make people more vulnerable to neurodegeneration in later life, and activated microglia may provide neuroprotection against amyloid buildup early in AD pathogenesis. Females might be more vulnerable to AD as a result of early-life microglial injury.
7	Masoud et al., 2016	Investigated the early postnatal exposure to Pb and alteration the expression of select miRNA (microRNA that Target Proteins Associated with Alzheimer's Disease).	Mechanistic-mice model	Mouse-Mother's milk	AD	Exposure to the heavy metal Pb in early life has a significant impact on the short- and long-term expression of miRNAs that target epigenetic mediators and neurotoxic proteins. Pb exposure increases miR-106b, miR-29b, and miR-132 expression initially. miR-106b decreases over time, while miR-124 is reduced. Pb exposure triggers changes in miRNA expression targeting AD-related proteins.
8	Lee and Freeman, 2016	Investigated the connection between latent neurological changes and embryonic Pb exposure utilizing the brains of adult male and female zebrafish.	Mechanistic-Zebrafish brain	Aquaria water	AD	Embryonic exposure to Pb at levels as low as 10 μg/L disrupts global gene expression patterns in a sex-specific manner that could lead to neurological alterations in later life. Embryonic Pb exposure in zebrafish leads to neurodegenerative gene expression changes. The Zebrafish model shows potential for studying neurodegenerative diseases.

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9	Wu et al., 2020	Investigated examined the possible mechanism by which Pb exposure exacerbates the development of Alzheimer's disease in mice by compromising the blood-brain barrier (BBB).	Mechanistic-mice model	Mice-Drinking water	AD	The potential mechanism by which early exposure to Pb causes the progression of AD has been examined in this study. The scientists found that Pb exposure can result in aberrant alterations in BBB junction proteins and hasten the deposition of Aβ1–42 in the brains of APP/PS1 mice. Additionally, it can raise p-tau expression in APP/PS1 and C57BL/6J mice. The equilibrium between Aβ generation and clearance is also disrupted by Pb exposure. The findings showed a connection between astrocytes and Aβ1–42 deposition in the brains of APP/PS1 mice.
10	Gu et al., 2020	Investigated the potential effects of long-term Pb exposure on the blood-brain barrier system's permeability using the Dynamic Contrast-Enhanced Computerized Tomography (DCE-CT) technique.	Mechanistic-mice model	Mice-oral gavage	AD	Data showed that Pb exposure increased the permeability surface area product, and significantly induced brain perfusion. However, Pb exposure did not alter extracellular volumes or fractional blood volumes in the mouse brain. The study suggests that Pb exposure at subtoxic and toxic levels directly targets the brain vasculature and damages the blood brain barrier system.
11	Bandaru et al., 2023	Investigated the precise mechanism by which Pb causes Alzheimer's disease, specifically mitochondrial damage, using human neuronal cells.	Mechanistic-human neuronal cells (SH-SY5Y)	human neuronal cells	AD	The results demonstrated that exposure to Pb increased oxidative stress by increasing MDA levels, lowering GSH levels, and lowering the expression of genes for antioxidants such as SOD2 (MnSOD) and Gpx4. In addition, cells treated with Pb showed decreased mitochondrial mass, MMP, ATP levels, cytochrome c oxidase activity, and mtDNA copy number. Additionally, it showed that treated cells had reduced expression levels of the protein markers NDUFS3, SDHB, UQCRC2, COX4, and ATP5A, indicating compromised mitochondrial respiration and subsequent mitochondrial dysfunction in Pb-induced AD. Thus, Pb toxicity may be a contributing factor to oxidative stress and mitochondrial dysfunction in the development of Alzheimer's disease.
12	Lee and Freeman, 2020	Investigated the relation between neurotoxic Pb exposure and de novo copy number alterations (CNAs) using Zebrafish fibroblast cells.	Mechanistic-Zebrafish cells	Cells	AD	The study found several genomic regions with CNAs brought on by in vitro Pb exposure, indicating that Pb exposure may act as an environmental chemical stressor that contributes to the development of de novo CNAs. There was a tendency for the number of CNAs to rise in proportion to Pb concentration. Amyloid precursor protein (APP), a crucial molecular target linked to the pathophysiology of Alzheimer's disease, is connected to nearly every gene in a molecular network. These data demonstrate that Pb exposure causes de novo CNAs, which may be a mechanism causing negative health effects linked to Pb toxicity, such as the pathophysiology

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						of neurological diseases, and warrant more research.
13	Liu et al., 2023	Investigated the effects of long-term lead exposure on the buildup of Aβ in cerebral capillaries and the expression of a vital Aβ transporter, low-density lipoprotein receptor protein-1 (LRP1), in brain parenchyma and capillaries in Sprague-Dawley rats.	Mechanistic-Rat model	Rat-oral gavage	AD	The cerebral vasculature naturally has a remarkably high affinity for the Aβ found in blood, as this study shows. Aβ buildup in the cerebral vasculature is significantly increased by Pb exposure, whether in vitro or in vivo. The reduced expression of an Aβ efflux carrier LRP1 in response to Pb in the studied brain region and fractions is partially responsible for this elevated Aβ accumulation.
14	Eid et al., 2018	Investigated early life Pb exposure and latent over expression of AD-related genes regulation histone activation pathways.	Mechanistic-mice model	Drinking water	AD	A lifetime reprogramming of gene expression brought on by early life exposure to Pb produces a global repression profile that may be mediated by both DNA methylation and histone modification pathways. Such reprogramming does not seem to occur in genes linked to Alzheimer's disease, and different epigenetic processes may mediate their latent overexpression.
15	Bihaqi et al., 2014	Investigated the expression of tau in the aged mice's brain cortex due to the infantile postnatal exposure to lead (Pb).	Mechanistic-mice model	Drinking water	AD	A rise in the levels of tau protein and tau mRNA is observed in aged mice that have been exposed to developmental Pb. An abnormal site-specific tau hyperphosphorylation along with increased levels of cyclin dependent kinase 5 (CDK5) was observed in aged mice that had previously been exposed to Pb. In addition, mice exposed to developmental Pb showed a changed p35/p25 protein ratio and increased serine/threonine phosphatase activity as old age. These modifications promoted an increase in tau phosphorylation, suggesting that environmental factors during development may play a role in neurodegenerative disorders.
16	Bihaqi et al., 2018	Investigated how developmental Pb exposure affected the α-Syn pathways in a mouse model that was knocked out for the murine tau gene and in a human neuroblastoma SHSY5Y cell line that had undergone exposure to a wide range of Pb doses.	Mechanistic-Mice and SHSY5Y cells	Drinking water	AD	Mice with early-life Pb exposure exhibit latent upregulation of α-Syn. Moreover, prior in vitro exposure to Pb increased the levels of Caspase-3, glycogen synthase kinase 3β (GSK-3β), and α-Syn and its phosphorylated forms. The latent effects of Pb exposure are mediated by epigenetic mechanisms.
17	Huang et al., 2024	Investigated the mechanism by which Pb exposure aggravates AD progression and	Mechanistic-mice model and BV-2 microglial cells	Drinking water	AD	The results of the study showed that long-term exposure to Pb can exacerbate memory and learning deficits in APP/PS1 mice. One possible explanation for the mechanism is that increased

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		the role of microglial activation, APP/PS1 mice and Aβ1-42-treated BV-2 cells were exposed to Pb.				expression of the mitochondrial protein CHCHD4/AIF in microglia, which causes mitochondrial copper overload through COX17-mediated translocation. This results in mitochondrial dysfunction and excessive mtROS accumulation, which in turn activates microglia.
18	Zhou et al., 2018	Investigated the role of cholesterol metabolism in lead induced premature AD-like pathology in rats.	Mechanistic-male Sprague-Dawley rats	Drinking water	AD	The findings showed that Pb exposure disrupted the metabolism of cholesterol in the brain, which led to early AD-like pathology in young, growing rats. Exposure to Pb disrupted the balance of cholesterol, reduced brain cholesterol, triggered the SREBP2-BACE1 pathway, reduced the expression of HMG-CR and LDL-R, and increased the expression of ABCA1 and LXR-α.
19	Ayyalasomayajula et al., 2019	Investigated the role of epigallocatechin gallate (EGCG) in reducing oxidative stress and apoptosis in human neural cells caused by Pb and β-APs, both alone and in combination.	Mechanistic-SH-SY5Y cells	Cells	AD	EGCG reduced oxidative stress caused by Pb and β-AP by scavenging reactive oxygen species, inhibiting annexin V and caspase-3, and lowering apoptosis through increased expression levels of Bax and Bcl2. EGCG mitigates oxidative stress and apoptosis to shield SH-SY5Y cells from the cytotoxicity caused by Pb and β-APs.
20	Lee et al., 2017	Investigated the impact of embryonic Pb exposure on AD genetic risk factors by analyzing sex-specific alterations in sorl1 expression in adult zebrafish.	Mechanistic-zebrafish	Aquaria water	AD	This study characterized sorl1 with changes in brain expression during aging being female-specific. No significant differences in sorl1 expression were observed with embryonic lead exposure. A zebrafish model was used to study AD genetic risk factors and sorl1. nSorl1 expression in the zebrafish brain was not influenced by age. The zebrafish model shows potential for AD research, with sorl1 characterization.
21	Lokesh et al., 2024	Investigated how Pb and amyloid β peptides (1–40 and 25–35) interact with cyclin-dependent kinase 5 (CDK5) and its activator, p25, to determine the molecular basis of Pb-induced neurotoxicity in neuronal cells and their possible neurodegenerative significance.	Mechanistic-Human SH-SY5Y cells	Cells	AD	The findings showed that Pb exposure caused changes in intracellular calcium and increased Pb absorption. Additionally, a significant decrease in overall antioxidant capacity and an increase in protein carbonylation, a hallmark of oxidative damage, were shown in the results, indicating a compromised ability of cells to fend off oxidative stress and increased oxidative damage to DNA. The role of Pb-induced CDK5-p25 signaling in AD pathogenesis was further supported by the observation of dysregulations in levels of calpain, p25-35, and CDK5, as well as markers linked to antioxidant metabolism (phospho-Peroxiredoxin 1), DNA damage responses (phospho-ATM and phospho-p53), and nuclear membrane disruption (phospho-lamin A/C). The complex molecular processes behind Pb-induced neurotoxicity are clarified by these findings, which also offer important new information about

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	the mechanisms underpinning the development of AD.

3.3.1. Mechanism of Pb-Induced AD Pathology in Mice/Cell Line

Mice serve as the predominant animal model for investigating the effects of Pb exposure on the brain, owing to the availability of transgenic mice predisposed to AD. A study by Wang et al. (2022) demonstrated that miR-124-3p/BACE1 pathway modulation is critically involved in Pb-induced AD-like amyloidogenic processing in Pb-exposed mice. Pb exposure contribute to the development of AD through several mechanism in experimental mouse model, including the elevation of tau protein and mRNA levels in aged mice (Bihaqi et al., 2014), reprogramming the expression of epigenetic intermediates involved in DNA methylation or histone modification that in turn regulate latent AD-related gene expression (Eid et al., 2016), early-life microglial damage and Amyloid accumulation (vonderEmbse et al., 2017), changes in miRNA expression targeting AD-related proteins (Masoud et al., 2016), elevated level of phosphorylated tau protein (p-tau), abnormal changes in BBB junction proteins, imbalanced the production and clearance abilities of Aβ (Wu et al., 2020). Pb exposure also increases permeability surface area product, affects brain perfusion and damage the blood brain barrier system (Gu et al., 2020), induces histone modification and DNA methylation (Eid et al., 2018), increases α-Synuclein, GSK-3β, Caspase-3 and tau hyperphosphorylation (Bihaqi et al., 2018), causes mitochondrial copper overload due to COX17-mediated translocation, mitochondrial dysfunction, excessive mtROS accumulation, microglia activation (Huang et al., 2024).

3.3.2. Mechanistic Insights from cell Line Studies

Researchers use several specific cell lines (i.e., SH-SY5Y, iPSCs, BV-2 microglial cells) in laboratory studies to model the Alzheimer's disease pathology, test potential treatments, and investigate the role of amyloid beta plaques, tau protein abnormalities, and other key features of AD in a controlled environment. These cell experiments are essential to understand the molecular mechanisms at the cellular level. In this review, we highlight seven studies that used different cell lines to investigate the AD pathobiology and molecular mechanism due to environmental Pb exposure. The reported molecular mechanisms of Pb exposure-related AD are inhibited APP translation and disruption of iron homeostasis (Rogers et al., 2016), PINK1/Parkin mediated mitophagy and dysfunctional mitochondria mediated apoptosis (Bandaru et al., 2022), altered calcium homeostasis, synaptic plasticity, elevated AD-like pathogenesis markers, including phosphorylated tau, tau aggregates, and Aβ42/40 (Xie et al., 2023), mitochondrial dysfunction and oxidative stress (Bandaru et al., 2023), mitochondrial dysfunction and excessive mtROS accumulation (Huang et al., 2024), oxidative stress and apoptosis (Ayyalasomayajula et al., 2019), oxidative stress mediated DNA damage, decrease in total antioxidant capacity and involvement of CDK5-p25 signaling (Lokesh et al., 2024).

3.3.3. Insights from Rat Models of Lead Exposure

The laboratory rat has been valuable model for brain research in disease model over the years. This review identifies two studies that examined the pathobiology of AD in relation to environmental Pb exposure using rat model. Zhou et al. (2018) demonstrated that Pb exposure contributed to early AD-like pathology in young growing rats by disturbing brain cholesterol metabolism, increasing Aβ accumulation and amyloid plaque deposition. Pb exposure impaired cholesterol homeostasis, decreased brain cholesterol levels, activated the SREBP2-BACE1 pathway, decreased HMG-CR and LDL-R expression and promoted the expression of LXR-α and ABCA1 (Zhou et al., 2018). In contrast, Liu et al. (2023) showed that chronic Pb exposure increased the affinity of Aβ40 to cerebral vasculature, intensified Aβ40 buildup and impaired LRP1 expression in both the brain parenchyma and vasculature (Liu et al., 2023).

3.3.4. Findings from Zebrafish Models of Lead Exposure

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Zebrafish model shows potential for studying neurodegenerative disease mechanisms like AD. Embryonic exposure to Pb at levels as low as 10 μg/L disturbed global gene expression patterns in a sex-specific manner, leading to neurological alterations later in life. Pb exposure during embryogenesis in zebrafish led to neurodegenerative gene expression changes (Lee and Freeman, 2016). In a study, examining the 12-month-old adult female and male zebrafish brain, exposed to either a control (0 μg/L) or 10 μg/L Pb only during embryogenesis (1-72 hours post-fertilization), gene ontology and pathway analysis demonstrated that both sexes had similar upper disease and functional categories, but female zebrafish exhibited 4.3 times more genetic alterations. Genes linked to the development and function of the nervous system were particularly more affected; adult females were found to have altered versions of 89 genes linked to AD, including sortlin-related receptor precursor (SORL1), apolipoprotein (APOE), and amyloid precursor protein (APP) (Lee and Freeman, 2016). Another study showed that environmental Pb exposure These CNAs are linked to AD outcomes with most genes are interconnected within a molecular network with amyloid precursor protein (APP), a crucial molecular target linked to the etiology of AD (Lee and Freeman, 2020).

3.4. Mechanisms and Pathobiology of AD Development Related to Cadmium Exposure

Cadmium (Cd) is a naturally occurring heavy metal that is bluish white in color and persistent in nature. The earth's crust serves as one of the natural sources of Cd, while anthropogenic sources include mining, refining, fossil fuel combustion, waste incineration, and other industrial activities such as manufacturing phosphate fertilizers (ATSDR, 2012). Cd is not an essential element; therefore, it has no physiological function in humans. However, according to the International Agency for Research on Cancer (IARC), Cd is classified as a Group-I carcinogen (cancer causing agent) and has numerous detrimental health effects upon exposure (Straif et al., 2009). Most cases of human exposure to environmental Cd through contaminated food, making diet the primary source of Cd exposure (Satarug et al., 2010). Additionally, People are exposed to Cd through inhalation, particularly by inhaling cigarette smoke which is another significant route of exposure. Chronic environmental Cd exposure increases the risks of various human diseases including kidney damage, high blood pressure, diabetes, decreased pulmonary function and osteoporosis (Satarug et al., 2010). Recently, Cd also has emerged as a neurotoxicant. Inhaled Cd can enter the brain through the olfactory bulb, and the blood cerebrospinal fluid barrier. Mechanistic studies have demonstrated that Cd exposure triggers oxidative stress, alters the permeability of the BBB, causes Aβ aggregation, produces tau neurofibrillary tangles, induces neuroinflammation and leads to apoptotic neuronal cell death (Bakulski et al., 2020).

This review delineates ten mechanistic laboratory studies concerning environmental Cd exposure and AD pathobiology. Among these ten studies, two utilized cell lines (SN56 and Neuro-2a cells), six employed mouse models, one was an experimental study, and one used a rat model to examine the association between environmental Cd exposure and AD pathobiology. Table 4 presents the primary findings and details of these ten mechanistic studies regarding the influence of Cd exposure on the pathways of AD development. Mouse models and cell culture treated with Cd exhibit mechanisms and symptoms of AD. However, the degree of influence of Cd exposure depends on several factors, including species, timing, dose, and length of exposure.

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Table 4. Literature summary of the mechanistic studies for Cadmium exposure and AD pathobiology.

SL	References	Study objective	Study type	Exposure	Outcomes	Key Findings
1	Liu, et al., 2023	Investigated the underlying mechanism and impact of low-dose environmental cadmium (Cd) exposure on the development of Alzheimer's disease.	Mechanistic-Mice-animal model	Mice-Drinking water	AD	At higher doses, Cd increased the amount of fluorescent dye that leaked and induced several degenerative morphological abnormalities in the mouse brains. The damage to the APP/PS1 mice was more severe than that of the C57BL/6J mice. Cd exposure cause a rise in anxiety-like behavior and disorderly movement, disruption to spatial reference memory, Aβ plaque formation in mice brains, an increase in microglia expression in the brain, and elevated levels of IL-6 in the cortex and serum.
2	Zhang et al., 2021	Investigated cadmium (Cd) interactions with ApoE4 gene variants to modify the gut-liver axis in mouse.	Mechanistic-Mouse model	Mice-Drinking water	AD	In ApoE4-KI males (the most vulnerable mouse strain to neurological damage), Cd exposure significantly altered the gut-liver axis. This was demonstrated by an increase in microbial AD biomarkers, a decrease in gut and blood pathways related to energy supply, and an increase in hepatic pathways involved in inflammation and xenobiotic biotransformation. Male ApoE4-KIs exhibited the most noticeable alterations in their gut microbiota, along with a predicted down-regulation of numerous vital microbial processes related to energy and nutrition homeostasis.
3	Wang et al., 2022	Investigated the effects of Cd-ApoE on the	Mechanistic-mice model	Mice-Drinking water	AD	One possible explanation for the variation in the sensitivity to Cd

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		transcriptome alterations in the livers and brains of ApoE3/ApoE4 transgenic mice.				neurotoxicity is that Cd dysregulated the brain and liver drug-processing genes in a way that was specific to sex and ApoE genotype. The livers of ApoE4 males exposed to Cd had more pro-inflammatory genes, and the brains of ApoE3 mice had more Cyp2j isoforms. Male-specific brain dysregulation of cation transporters was observed.
4	Notarachilleet al., 2014	Investigated the effects of varying concentrations of Cd on the secondary structure of AbP1–42 in an aqueous environment as well as on the AbP1–42 ion channel integrated in a planar lipid membrane composed of phosphatidylcholine with 30% cholesterol.	Mechanistic-Experimental	-	AD	Results reinforce and broaden the growing idea that AD and environmental pollutants like Cd are related. By acting on both the channel integrated into the membrane and the peptide in solution, Cd can interact with the AbP1–42 peptide, reducing AbP1–42 channel activity and turnover until the channel activity completely vanishes and forming large amorphous aggregates in solution that are prone to precipitation. The production and neurotoxicity of AbP fibrils or oligomers may be significantly influenced by Cd.
5	Matsushita et al., 2023	Investigated the possibility of functionally rescuing ApoE4-KI mice's Cd-induced cognitive impairment through genetic and conditional activation of adult neurogenesis.	Mechanistic-mice model	Drinking water	AD	The study showed a clear correlation between memory impairment and adult neurogenesis in a GxE model of ApoE4 by finding that Cd-induced impairments in hippocampus-dependent short-term spatial memory were restored by selective and conditional stimulation

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						of adult neurogenesis. The results offer compelling proof of a GxE effect and a plausible underlying mechanism involving adult neurogenesis at levels of Cd exposure that are applicable to the US population.
6	Del Pino et al., 2016	Investigated the mechanisms of cell death induced by cadmium (Cd) on basal forebrain cholinergic neurons.	Mechanistic-SN56 Cell lines	SN56 cholinergic mourine septal cell line	AD	By blocking the M1 receptor, overexpressing AChE-S and GSK-3β, downregulating AChE-R, and raising the levels of Aβ, total, and phosphorylated tau proteins, Cd causes cell death in cholinergic neurons. The findings of this study offer new insight into the processes behind the detrimental effects of Cd on cholinergic neurons and imply that Cd may mediate these processes by blocking M1R through altered expression of AChE splices.
7	Deng et al., 2024	Investigated examined the underlying mechanism and impact of autophagy on the development of AD caused by environmental Cd.	Mechanistic-Mouse neuroblastoma cells (Neuro-2a cells)	Cells	AD	RAB7A desuccinylation, which is catalyzed by SIRT5, is a crucial adaptive mechanism that helps address AD-like pathology and Cd-induced autophagic flux blockage. SIRT5 made RAB7A more active by desuccinylating it at the Lys31 residue. RAB7A activation acted as a buffer against autophagic flux blockage, hence reducing the worsening of AD-like pathologies and cognitive impairment caused by Cd.
8	Arab et al., 2023	Investigated the potential of topiramate to combat the	Mechanistic-Rats model	oral gavage	AD-Cognitive Deficits	The effectiveness of topiramate in improving behavioral outcomes, such as memory/learning

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		cognitive deficits induced by cadmium in rats with an emphasis on hippocampal oxidative insult, apoptosis, and autophagy.				impairments and histopathological abnormalities, as well as certain molecular processes related to hippocampus disruptions of redox milieu, apoptosis, and autophagy, were the primary focus of this investigation. Hippocampal GLP-1 was markedly restored by topiramate, which also attenuated p-tau and A42. Notably, it increased GABA and cholinergic neurotransmitters and markedly decreased glutamate concentration in the hippocampus. The SIRT1/Nrf2/HO-1 axis was significantly activated, and the hippocampus suppressed the pro-oxidant processes, which led to the behavioral recovery. Additionally, topiramate suppressed the apoptotic alterations in the hippocampus and deactivated GSK-3. Within Topiramate's pro-autophagic, antioxidant, and anti-apoptotic characteristics helped explain its neuroprotective effects in Cd-intoxicated rats. As a result, it might help lessen cognitive impairments brought on by Cd.
9	Zhang et al., 2020	Investigated the gene-environment interactions (GxE) between ApoE-e4 and Cd exposure on cognition, a mouse model of AD was used that expresses	Mecahnistic-Mouse model	Mouse-Drinking water	AD	A GxE between ApoE4 and Cd exposure causes accelerated cognitive deterioration, and one of the possible underlying mechanisms is reduced adult hippocampus neurogenesis.

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		human ApoE-e3 (ApoE3-KI [knock-in]) or ApoE-e4 (ApoE4-KI).				Additionally, during the early stages of the animals' lives, male mice were more vulnerable to this GxE impact than female mice.
10	Qian et al., 2024	Investigated the involvement of cellular senescence in AD, the effects of one of the potential environmental risk factors for AD, cadmium chloride (CdCl2) exposure was explored on neuron senescence *in vivo* and *in vitro.*	Mechanistic-Mice and SHSY5Y cells	Mice-Drinking water	AD	Cd promoted neural senescence via cascade activating the p53/p21/Rb pathway. SigmaR1 depletion contributed to neural senescence through Ca^{2+} dyshomeostasis and mitochondrial dysfunction. Cd activated SEL1L/HRD1-mediated ERAD to degrade SigmaR1 via ubiquitination at its K142 site. SEL1L/HRD1-regulated SigmaR1 degradation and p53/p21/Rb pathway was activated in AD. SigmaR1 agonist ANAVEX2-73 attenuated Cd-induced AD-like phenotype via the restrain of neural senescence. A new senescence-associated regulatory pathway for the SEL1L/HRD1/SigmaR1 axis that influences the pathological development of AD linked to CdCl2 exposure was identified in this study. Pharmacological stimulation of SigmaR1 may be a viable intervention technique for AD therapy, and it may serve as a neuroprotective biomarker of neuronal senescence.

3.4.1. Insights from Mouse Models of Cadmium Exposure

Mouse models have shown promise in the neurological research field and providing insights into the molecular mechanisms underlying environmental Cd exposure and AD pathobiology. While oxidative stress, neuroinflammation, and apoptotic neuronal cell death are well-established

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molecular pathways involved in cadmium (Cd) exposure and AD pathobiology, emerging mechanisms continue to be identified over time. This current review identifies six mouse model studies related to environmental Cd exposure and its contribution in AD pathways. Among these studies, one explored the effects of low-dose environmental Cd exposure on AD progression and underlying mechanism using wild type C57BL/6J and APP/PS1 double transgenic mice. The findings are noteworthy as both genotypic (C57BL/6J and APP/PS1) exhibited similar Cd levels in the blood after exposure to the same Cd dose, yet the toxic effects differed in genotypes. Environmental Cd exposure exerts more severe damage in APP/PS1 mice compared to C57BL/6J mice, leading to increased anxiety-like behavior, chaotic movement, spatial reference memory damage, Aβ plaque deposition and microglial activation in the brain, as well as increased expression of IL-6 in the cortex and serum. These results indicate that low-dose environmental Cd exposure contributes to AD progression through mechanisms, including BBB disruption, increased Aβ production, reduced Aβ clearance and increased inflammatory responses (Liu, et al., 2023). Other potential molecular mechanisms of Cd exposure-induced AD progression include genotype- and gender-specific gut dysbiosis, increased microbial AD biomarkers, reduced energy supply-related pathways in gut and blood, and enhanced hepatic pathways involved in inflammation and xenobiotic biotransformation (Zhang et al., 2021).

In another study, Wang et al. (2022) demonstrated that Cd dysregulated brain and liver drug-processing genes in a sex- and ApoE-genotype specific manner, contributing to variations in susceptibility to Cd neurotoxicity. Proinflammatory genes were enriched in Cd-exposed ApoE4 males' livers while Cd up-regulated Cyp2j isoforms in the brains of ApoE3 mice. Dysregulation of cation transporters was male-specific in the brains. Matsushita and colleagues investigated the genetic and conditional stimulation of adult neurogenesis and its rescue role in Cd-induced cognitive impairment in ApoE4-KI mice (Matsushita et al., 2023). They showed that specific and conditional stimulation of adult neurogenesis rescued Cd-induced impairments in hippocampus-dependent short-term spatial memory in a gene-environment interactions (GxE) model of ApoE4 and Cd exposure, demonstrating a direct link between memory impairment and adult neurogenesis in the GxE mice model (Matsushita et al., 2023).

Similarly, Zhang et al. (2020) revealed that a GxE between ApoE4 and Cd exposure accelerates cognitive impairment with impaired adult hippocampal neurogenesis identified as potential mechanism. Furthermore, male mice were more susceptible than female mice to the GxE effect during youth (Zhang et al., 2020). Qian et al. (2024) reported that Cd promotes neural senescence by activating the p53/p21/Rb pathway. Their findings revealed that SigmaR1 depletion contributed to neural senescence through Ca2+ dyshomeostasis and mitochondrial dysfunction. This mouse model-combined with SHSY5Y cell culture studies revealed a novel senescence-associated regulatory route for the SEL1L/HRD1/SigmaR1 axis that affects the pathological progression of Cd exposure-associated AD. The study concluded that SigmaR1 functions as a neuroprotective biomarker of neuronal senescence, and pharmacological activation of SigmaR1 could serve as a promising therapeutic strategy for AD.

3.4.2. Mechanistic Insights from Cell Line of Cadmium Exposure

Cell culture studies are crucial for elucidating the molecular mechanism and cellular pathways associated with environmental risk factors and AD pathobiology. Several cell lines, including AD Pathophysiology Model (i.e., induced pluripotent stem cells (iPSCs), SH-SY5Y, PC12, and primary neuronal cultures) are commonly used as models of AD pathophysiology to study the molecular mechanism of AD progression and the contribution of the environmental factors. In this review, two in vitro studies using SN56 and Neuro-2a cells were identified for review and thoroughly discussed. Deng et al. (2024) carried out an in vitro study using mouse neuroblastoma cells (Neuro-2a cells) to investigate the effect of autophagy on environmental Cd-induced AD progression and the underlying molecular mechanisms. Their findings revealed that Cd exposure disrupted autophagosome-lysosome fusion and impaired lysosomal function, leading to defects in autophagic clearance

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followed by APP accumulation and nerve cell death (Deng et al., 2024). Their study also demonstrated that SIRT5 is an essential molecular target in Cd-impaired autophagic flux. Mechanistically, Cd exposure reduced SIRT5 expression, increasing the succinylation of RAB7A at lysine 31 and inhibiting RAB7A activity, which contributed to autophagic flux blockade. This indicates that SIRT5-catalysed RAB7A desuccinylation is an essential adaptive mechanism for the amelioration of Cd-induced autophagic flux blockade and AD-like pathogenesis (Deng et al., 2024). Del Pino et al. (2016) investigated the mechanism of Cd exposure-induced basal forebrain cholinergic neurons cell death. They showed that Cd induces cell death on cholinergic neurons through the blockade of M1 receptor, overexpression of AChE-S and GSK-3β, down-regulation of AChE-R and increase in Aβ and total and phosphorylated tau protein levels (Del Pino et al., 2016).

3.4.3. Findings from Rat Models of Cadmium Exposure

Arab et al. (2023) investigated the Cd-induced neurotoxicity mechanisms and examined the potential neuroprotective role of topiramate against Cd-induced cognitive deficits in rats, with an emphasis on hippocampal oxidative insult, apoptosis, and autophagy. They found that Cd exposure triggered spatial learning/retention memory impairments, deterioration of the recognition memory, increased hippocampal neurodegeneration signals (elevated hippocampal levels of Aβ42 and p-tau), augmented hippocampal glutamate content, and altered the SIRT1/Nrf2/HO-1 axis and AMPK/mTOR signaling pathway (Arab et al., 2023).

4. Discussion

The growing body of research into environmental toxins has highlighted the significant role that metals such as arsenic (As), manganese (Mn), lead (Pb), and cadmium (Cd) play in the development and progression of neurodegenerative diseases, particularly Alzheimer's disease (AD). These toxicants induce a range of pathological processes that intersect with well-known mechanisms of AD, such as oxidative stress, mitochondrial dysfunction, protein aggregation, and neuroinflammation. The studies reviewed here provide a deeper understanding of how these elements contribute to AD and suggest potential pathways for therapeutic intervention.

Arsenic exposure has long been recognized for its carcinogenic properties, but emerging evidence has also linked it to neurodegenerative diseases like AD. Chronic exposure to arsenic in animal models results in mitochondrial dysfunction, tau hyperphosphorylation, and amyloid-beta (Aβ) accumulation—key features of AD pathology. These effects are coupled with disruptions in memory, circadian rhythms, and neuroinflammation, all of which are hallmarks of neurodegenerative conditions. Mechanistically, arsenic has been shown to interact with critical protein kinases such as GSK3β and ERK1/2, leading to tau aggregation and the exacerbation of Aβ accumulation. These insights position arsenic as an environmental risk factor that could significantly contribute to the development of AD in exposed populations.

Similarly, manganese toxicity has been implicated in the pathogenesis of neurodegenerative diseases, particularly through its effects on glutamate regulation and neuroinflammation. Manganese exposure leads to the suppression of the glutamate transporter EAAT2, resulting in excitotoxicity and neuroinflammation. This dysregulation contributes to synaptic dysfunction, cognitive deficits, and abnormal amyloid precursor protein (APP) processing. The disruption of autophagy, an essential cellular process for clearing damaged proteins, further exacerbates the pathological effects of manganese. Research also suggests that transcription factors like REST may play a protective role against Mn-induced neurotoxicity by modulating oxidative stress and inflammation, offering potential therapeutic strategies (Figure 3).

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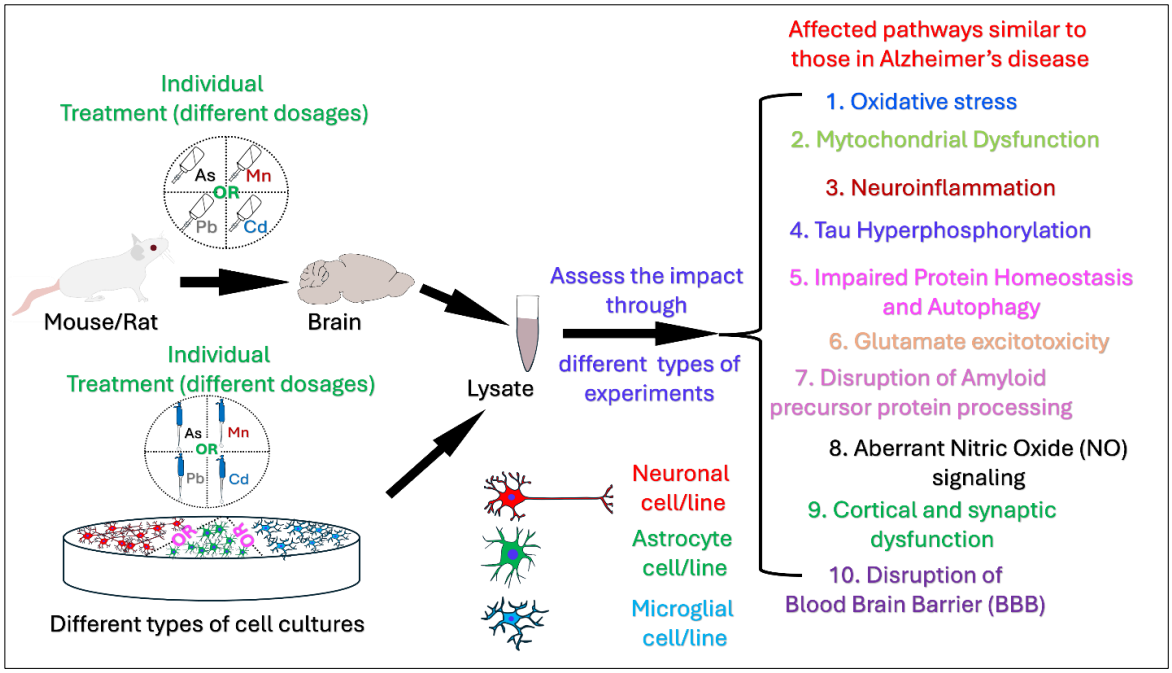

Figure 3. Summarized findings of discussed mechanistic studies. Using animal and cell line studies, it was observed that while exposure to individual metals (As, Mn, Pb, Cd) shares some affected pathways—such as oxidative stress, mitochondrial dysfunction, impaired protein homeostasis, autophagy dysfunction, and Tau hyperphosphorylation—certain effects are unique to specific metals. For example, Pb and Cd induce Blood-Brain Barrier (BBB) disruption, whereas As and Mn are associated with neuroinflammation, glutamate excitotoxicity, impaired Amyloid Precursor Protein processing, aberrant Nitric Oxide (NO) signaling, and cortical and synaptic dysfunction.

Lead and cadmium, while historically associated with other toxicological concerns, have more recently emerged as significant neurotoxicants linked to AD. Lead exposure disrupts calcium homeostasis, synaptic plasticity, and mitochondrial function, processes that are integral to the development of neurodegenerative diseases. Lead's ability to induce oxidative stress and epigenetic reprogramming further exacerbates its neurotoxic effects. On the other hand, cadmium has been shown to activate the p53/p21/Rb pathway, inducing neural senescence, while also disrupting gut-brain interactions and aggravating neuroinflammation. Both lead and cadmium impair autophagic flux and mitochondrial function, leading to cellular dysfunction and contributing to AD pathology (Figure 3).

These studies underscore the importance of considering both genetic predispositions and environmental exposures in understanding AD. Research using a variety of models, including mouse, rat, and zebrafish models, has significantly advanced our understanding of how environmental toxins contribute to AD. These models offer insights into sex-specific differences, genotype-environment interactions, and the molecular pathways through which these toxins exert their effects. However, several gaps remain in our understanding of the chronic, low-level exposure scenarios that are more typical of real-world environments. Moreover, the variability in genetic and environmental contexts across studies complicates efforts to generalize findings.

5. Conclusions and Future Directions

The evidence presented here clearly points to arsenic, manganese, lead, and cadmium as critical environmental risk factors for the development and progression of Alzheimer's disease. These metals disrupt essential brain processes such as oxidative stress regulation, mitochondrial function, and autophagy, all of which contribute to neurodegeneration. Arsenic's impact on tau phosphorylation and amyloid-beta accumulation, manganese's role in glutamate dysregulation and excitotoxicity, and

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the effects of lead and cadmium on mitochondrial bioenergetics and cellular senescence highlight the intricate molecular mechanisms through which these toxicants contribute to AD.

While animal and cell line studies have provided invaluable insights into the molecular and cellular underpinnings of metal-induced neurotoxicity, further research is needed to address existing gaps. A more comprehensive understanding of the cumulative effects of chronic, low-level exposure to these toxicants, particularly in the context of genetic susceptibility, is essential for developing targeted therapeutic strategies. The complexity of Alzheimer's disease necessitates a holistic approach that integrates environmental, genetic, and epigenetic factors.

5.1. Future Directions

Future research should prioritize several key areas to enhance our understanding of the environmental contributions to Alzheimer's disease and identify potential interventions.

Longitudinal and Epidemiological Studies: Large-scale studies that assess the cumulative effects of arsenic, manganese, lead, and cadmium exposure on neurodegeneration are essential. These studies should be designed to track exposure levels over time and examine their correlation with cognitive decline and AD incidence. Epidemiological data will provide critical insights into the dose-dependent effects of these metals and their role in the progression of AD in human populations.

Mechanistic Studies: Further research is needed to explore the interaction between environmental exposures and genetic susceptibility to AD. For example, studies could investigate how genetic risk factors such as APOE4 interact with metal-induced oxidative stress, inflammation, and mitochondrial dysfunction. Understanding these interactions could reveal novel biomarkers for early diagnosis and targeted therapeutic interventions.

Therapeutic Development: Targeting the molecular pathways affected by arsenic, manganese, lead, and cadmium exposure could lead to the development of new therapeutic strategies for AD. Inhibitors of kinases like GSK3β and ERK1/2, which are involved in tau phosphorylation and aggregation, could be explored as potential treatments. Additionally, enhancing the function of transcription factors like REST, which may protect against metal-induced neurotoxicity, could offer a novel therapeutic approach.

Intervention Studies: Investigating the protective effects of antioxidants, chelating agents, and epigenetic modulators may provide strategies to counteract the neurotoxic effects of these metals. Compounds that restore glutamate transporter function or enhance mitochondrial resilience could mitigate excitotoxicity and bioenergetic deficits, potentially providing therapeutic benefits.

Environmental Policy and Public Health: Translating research findings into actionable policies is crucial for mitigating the impact of environmental toxins on public health. Efforts to regulate arsenic, manganese, lead, and cadmium levels in drinking water and food sources, coupled with public education campaigns, could reduce exposure and the associated risks of neurodegenerative diseases. Stronger environmental regulations and improved waste management practices are key to preventing further contamination.

Advanced Models: The use of organoid models and humanized systems will improve the translational relevance of findings. These models can better replicate human-specific aspects of AD pathology and allow for high-throughput screening of potential interventions. By advancing animal models that more closely mimic human AD, we can enhance the ability to translate preclinical findings into clinical applications.

In conclusion, addressing the environmental contributions to Alzheimer's disease, particularly from arsenic, manganese, lead, and cadmium exposure, is essential for mitigating the growing public health burden of neurodegenerative diseases. By integrating mechanistic studies, longitudinal research, and public health initiatives, we can improve our understanding of these environmental risk factors and develop more effective strategies for prevention and treatment.

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resources, G.A. and K.M.K.; data curation, K.M.K.; writing—original draft preparation, G.A. and M.S.R.; writing—review and editing, K.M.K.; visualization, M.S.R and G.A.; supervision, G.A. and K.M.K.; project administration, G.A. and K.M.K. All authors have read and agreed to the published version of the manuscript.

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