DOI: 10.53469/jcmp.2025.07(03).19

Progress of Lead-induced Mechanisms of Nervous System-related Diseases in the Field of Molecular Biology

Qian Wang, Zengguo Wang*, Jian Feng, Xiaofeng Xiong

Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
**Correspondence Author*

Abstract: ***Lead is a toxic heavy metal associated with significant global health burdens, particularly in developing countries. This review synthesizes current molecular mechanisms of lead-induced neurotoxicity, focusing on oxidative stress, neuroinflammation, and the microbiota-gut-brain axis. Lead disrupts redox homeostasis, induces neuroinflammation via TLR4/MyD88-NF-κB signaling, and dysregulates gut microbiota, contributing to cognitive deficits and neurodegenerative risks. Emerging therapeutic strategies targeting these pathways offer novel insights for mitigating lead-related neurological disorders.***

Keywords: Lead, Neurotoxicity, Neuroinflammation, Oxidative stress**.**

1. Introduction

Lead is a naturally occurring toxic metal in the Earth's crust, primarily existing as divalent metallic ore. Its use dates back over 5,000 years, attributed to its high density, corrosion resistance, low melting point, and malleability, which have enabled widespread applications in industries such as manufacturing, construction, and traditional crafts. Additionally, lead is utilized in pigments, paints, jewelry, cosmetics, and certain traditional toys. In China, lead pollution primarily stems from primary lead smelting, lead-acid battery waste, and lead-containing oil [1]. Despite advancements in human civilization and growing awareness of lead's unique toxicity, its prolonged and diverse applications have led to severe global environmental contamination, making potential lead exposure a non-negligible public health concern.

Lead is characterized by a slow clearance rate and high resistance to degradation. It is primarily absorbed by humans through the respiratory tract, gastrointestinal tract, and dermal absorption, accumulating preferentially in bones, blood, liver, kidneys, and reproductive organs. This accumulation can induce multi-system damage, with particularly potent selective toxicity toward the central nervous system (CNS). Compared to individuals exposed postnatally, children exposed to lead prenatally are more vulnerable to its toxic effects during development [2]. Lead crosses the placenta and blood-brain barrier, accumulating in the brain to alter neural architecture, synaptic formation, transmission, and cell survival [3], leading to emotional and learning disorders. Chronic lead exposure is also a recognized risk factor for neurodegenerative diseases such as Alzheimer's, with early-life lead exposure increasing the risk of late-life dementia and severe impairments in learning, memory, and cognitive function. Current evidence indicates that lead exerts toxicity via mechanisms including oxidative stress, apoptosis, calcium homeostasis disruption, and autophagy induction [4]. However, the precise molecular pathways remain incompletely understood. Advances in molecular biology have provided powerful tools for analyzing brain activity and neurotoxic mechanisms, driving substantial efforts globally to uncover novel approaches for understanding lead neurotoxicity. These insights not only offer new strategies for preventing lead poisoning but also advance molecular biology through translational research. This review summarizes current findings on lead-induced neurotoxicity from the perspective of medical molecular biology.

2. Research Progress on Lead Neurotoxicity in the Field of Molecular Biology

The research hotspots at home and abroad mainly focus on the neurotoxic mechanism of lead. According to literature review, its research can be roughly divided into studying the neurotoxic effects directly caused by lead exposure and the effects on the growth and development process of offspring due to lead exposure during pregnancy according to different research objects. It is often seen to use rats for modeling to study behavioral and cognitive impairments of themselves or their offspring. The research on the toxicity mechanism caused by lead exposure emerges in endlessly, and attempts are made to see whether a certain target can reverse the neurodegenerative changes caused by lead exposure.

2.1 Oxidative Stress

Lead exposure causes the body to produce excessive reactive oxygen species, breaking the redox balance in the body and can lead to lipid peroxidation, DNA damage and destruction of the cellular antioxidant defense system. The oxidative damage effect induced by lead is mainly through two independent but interrelated mechanisms. First, as mentioned above, excessive reactive oxygen species are produced. In this mechanism, MDA (malondialdehyde) is an important biomarker of free radical damage in oxidative stress reactions commonly used. In previous studies, it was found that tissue lipid peroxides increase or the inherent antioxidant defense decreases. The significant increase in MDA may be due to in vitro culture of linolenic acid, linolenic acid and arachidonic acid, and in vitro experiments with lead. The level of MDA produced is related to the ratio of double bonds in fatty acids, indicating a possible relationship with the peroxidation process. The potential mechanism of this change in the fatty

acid composition of membranes and Pb+2 is related to in vitro phosphatidylcholine membranes. In general, this interaction indicates that changes in the lipid composition of membranes may lead to changes in membrane integrity, permeability and performance, which enhances the vulnerability of lipid peroxidation [5]. In terms of membrane integrity, some studies have shown that maternal lead exposure can affect the learning and memory of offspring through GLUT4 membrane translocation. Glucose is one of the main neuromodulatory mechanisms for brain learning and memory. The latest research shows that lead exposure can lead to glucose tolerance and insulin resistance. Thus, the "hippocampal hypothesis" is proposed, that is, it is believed that cognitive activities will deplete extracellular glucose in hippocampal cells, while exogenous glucose can reverse this depletion. Researchers such as Zhao Zaihua [6] used the water maze test to prove that maternal lead exposure does damage the spatial learning and memory ability of offspring. PET-CT (positron emission tomography computer) is used to measure the sugar oxidation of the hippocampus [4, 5].

2.2 Neuroinflammation

Neuroinflammation caused by lead exposure is also a research hotspot of lead toxicity mechanism at home and abroad. Firstly, lead has been proven to activate the TLR4/MyD88 pathway by regulating the NF-kβ signaling pathway [7]. Therefore, the increase of inflammatory cytokines in the central nervous system may be derived from the activation of microglia and astrocytes induced by lead, leading to neuronal damage. Microglia are inherent immune cells in the central nervous system and participate in brain development, neural environment, damage response and repair. According to research, microglia have two polarization methods. One is the classical activation pathway, that is, the M1 phenotype: releasing TNF-α, IL-6, IL-1β, etc., and promoting inducible nitric oxide synthase (iNOS), NADPH oxidase 2. (NADPH oxidase 2, NOX2), chemokine receptor 7 (CCR7) and other high expressions [8]. Among them, TNF-α can be secreted through microglia-related NFκB activation. Activated NFκB can activate more TNFα. The NFκB pathway, together with other intracellular signaling pathways (such as p38 MAPK and JAK-STAT pathways), produces TNF-α [5], thereby exacerbating the inflammatory response, destroying the blood-brain barrier, and accelerating the death of neurons. The second is the alternative activation pathway, that is, the M2 phenotype. It releases transforming growth factor-β (TGF-β), interleukin-10 (IL-10), etc., inhibits the inflammatory response, promotes neuronal repair and plays a role in protecting neurons. Triggering receptor expressed on myeloid cells 2. (triggering receptor expressed on myeloid cells 2, TREM2) participates in microglia activation and is specifically expressed on the microglia cell membrane, promoting the transformation of microglia to M2 type. Some studies have shown that TREM2 is regulated by microRNAs. The regulation of (microRNAs, miRNAs) [9]. Exosomes are released by various neurons, glial cells, vascular endothelial cells, etc. in the central nervous system. Studies have shown that miR-124 secreted by microglia after traumatic brain injury can regulate the occurrence of neuronal inflammation. Exosomal microRNA plays an important role in the occurrence and development of neuroinflammation and neurodegenerative diseases, and is involved in the occurrence and development of neurodegenerative diseases such as Alzheimer's disease. Long-term chronic lead exposure can also cause Alzheimer's disease-like nerve damage. Studies have shown that lead exposure can lead to changes in the expression profile of serum exosomal microRNA, among which the expression changes of miR-124 and miR-506 are more significant. In the study, Bo used high-throughput sequencing difference methods for exosomal transcriptome sequencing and bioinformatics analysis to screen out key differentially expressed microRNAs, namely miR-124 and miR-506. Then, the Realtime-PCR method was used to verify the expression of differential microRNAs in exosomes, and then relevant analysis was applied to analyze the correlation between the expression of serum exosomal miR-124 and miR-506 and changes in neuroinflammation and neurobehavior. Finally, hierarchical regression analysis was applied for mediation effect analysis. It was found that differentially expressed exosomal miR-124 and miR-506 played a partial mediating effect in lead exposure-induced neurobehavioral changes, emotional state changes, and serum IL-1β, and the two played a complete mediating effect in lead exposure-induced increase in serum TNF-α. Among them, miR-124 can activate the JAK/STAT signaling pathway by targeted inhibition of SOCS3 expression, thereby releasing IL-1β and TNF-α and promoting neuroinflammatory damage. This study suggests a new miR-124 target for preventing nerve damage caused by lead exposure [10]. Furthermore, lead can interfere with the function of astrocytes, making the functions of microglia and astrocytes synergistic. For example, after lead exposure, microglia are activated to induce the production of inflammatory cytokines, and astrocytes secrete them into the surrounding tissues, thereby mediating the immune response and aggravating the damage to the blood-brain barrier and neurons [11]. However, more extensive research is still needed on its participation in the brain neuroinflammation pathway by glial cells to find more operating targets for preventing and treating human lead poisoning.

Second, necrosis is related to inflammatory reactions. People have long believed that necrosis is a passive death caused by pathology. More and more evidence shows that the death form called necrosis is similar to apoptosis in vivo and is mediated by cellular processes [12]. Their common point is that a single signaling system using Ca2+ as a universal messenger is regulated [13]. The difference is that apoptosis is considered non-immune and it does not trigger inflammation. However, necrosis directly triggers inflammation by massively releasing damage-associated molecular patterns (DAMPs) from disintegrating cells [14]. This death mode is mainly driven by the activation of TNF-α, and TNF-α involves receptors. Interacting serine-threonine kinase 1 (RIP1), RIP3, and mixed lineage kinase domain-like (MLKL) [15]. Necrosis mediated by receptor-interacting protein kinase-3 (RIPK3) and its substrate MLKL is the best characterized form of regulatory necrosis [14]. Increasing evidence points to a critical role for necrosis in inflammation, and it is therefore believed that necrosis is also involved in lead-induced neuroinflammatory responses [4].

For other potential mechanisms of neuroinflammation caused by lead exposure, studies have shown the role of inflammasomes in lead toxicity, confirming that the NF-κB

pathway and autophagy process play a role in lead-induced NLRP3 activation in neuroinflammation [16]. In the study of the SIRT1/HMGB1/NF-κB pathway in lead-induced neuroinflammation in the cerebral cortex of rats, it was found that sodium para-aminosalicylate (PAS-Na) reduced the increase in Pb-induced TNF-α and IL-1β levels, mediated a significant increase in SIRT1 and BDNF levels, a decrease in HMGB1 and phosphorylation of p65 NF-κB expression, proving the anti-inflammatory effect of PAS-NA on cortical neuritis [17]. In addition, dietary fiber, as a natural product, also has a certain anti-inflammatory effect. Lead can cause disorders of transgenic species and lose homeostasis of immune function. Studies have found that dietary fiber and its metabolites can slow down lead-induced neuroinflammation by inducing changes in transgenic species and quantities and regulating the immune system [18]. These findings enrich the existing mechanisms of neuroinflammation caused by lead exposure and provide more clues for us when facing diseases caused by lead exposure.

2.3 Microbiome-gut-brain Axis

It should be known that the intestine is the first organ to come into direct contact with oral lead. Therefore, research on the potential toxicity of lead exposure to the intestinal flora and intestinal barrier damage has also been a hot topic in recent decades, and microbiology and neuroscience are becoming increasingly closely related. The intestinal flora can affect the nervous system through pathways such as the vagus nerve, immune nerve, and flora metabolites. Moreover, the intestinal microbiota is also an important physical barrier against the toxic effects of heavy metals [19]. The intestinal physical barrier is composed of epithelial cells connected by tight junction proteins (TJ), which can prevent the entry of xenobiotics. Zhai's [19, 20] research has proved that oral lead exposure can reduce the relative expression of colonic TJ in mice, including zonula occludens-1 (ZO-1) and occludin, thereby increasing paracellular permeability in the intestine. ZO-1 and occludin play a crucial role in maintaining the permeability of the intestinal barrier. Zhu [21] observed the effects of lead exposure on the neurobehavior and intestinal flora structure of mice. Through sequencing monitoring, it was found that the abundance of the phylum Proteobacteria increased relatively at the phylum level, while the ratio of the intestinal dominant bacteria Bacteroidetes and Firmicutes decreased with the increase of lead exposure dose [22]. Zhu's research shows that at the genus level, the abundances of Desulfovibrio, Lachnospiraceae, and Turicibacter increase in the high lead exposure group. Previous studies have found that Desulfovibrio and Turicibacter are inflammatory bacteria genera, which also increase in AD mice in addition to enteritis. It is inferred that they are related to neuroinflammation [23]. Therefore, it is proposed that chronic lead exposure may cause intestinal flora imbalance, and the changes of some bacteria may be related to learning and memory ability [22]. It is speculated that the disorder of intestinal flora caused by lead is related to lead neurotoxicity, suggesting a new way of lead toxicity. The concept of the microbiota-gut-brain axis indicates that the resident microbiota can have a considerable impact on host behavior. There is evidence that probiotics are related to lead-induced cognitive impairment by reshaping the intestinal microbiota of lead-exposed rats. However, in order to further understand the pathways by which specific strains affect the gut-brain axis and repair lead-induced cognitive impairment, some studies have focused on Lactobacillus rhamnosus (GR-1). GR-1 is a Gram-positive bacterium of the genus Lactobacillus, with high intestinal adhesion rate and strong colonization ability. At the same time, it acts as a biological barrier and can also regulate the balance of the host's intestinal flora and improve the body's immunity. Therefore, Gu [24] and others studied the relationship between intestinal flora and lead-induced cognitive impairment after administration of GR-1. Through the water maze test, it was found that the species-specificity of GR-1 can alleviate lead-induced learning and memory deficits. After supplementing GR-1 and performing 16S rDNA sequencing, it was found that GR-1 can restore the specific microbiota of lead-exposed rats. Further fecal microbiota transplantation shows that GR-1 can slow down lead-induced learning and memory deficits by reshaping the intestinal microbiota. In the GR-1 treatment group, rats showed reduced lead-induced damage to the integrity of the intestinal barrier and decreased microglia and inflammatory factors in the hippocampus as seen by colon HE staining and enzyme-linked immunosorbent assay (ELISA). Finally, quantitative research on the axons of P12 cells found that granulocyte colony-stimulating factor (G-CSF) plays a key role in lead-induced neurotoxicity. It is believed that GF-1 rescues lead-induced neurotoxicity by promoting the expression of the anti-inflammatory factor G-CSF. Although G-CSF is not the only key factor regulating cognitive deficits caused by lead exposure. However, the study by focusing on reshaping the gut-brain axis suggests that we can improve cognitive deficits caused by chronic lead exposure through long-term probiotic intervention and contribute to the treatment strategy for lead-induced neurotoxicity.

Lead exposure can cause not only cognitive and behavioral deficits such as impairment of memory and learning ability but also depressive-like behavioral changes [25]. As disciplines continue to advance, more and more biological evidence reports that intestinal flora not only participates in the physiological functions of the body. The regulation also participates in the regulation of neuropsychiatric diseases through the microbiota-gut-brain axis [26]. With the in-depth study of microbial genes and the application of bioinformatics in microbial communities, it is found that depression may be caused by intestinal flora problems [27]. Serotonin (5-HT) is a neurotransmitter distributed in the central nervous system and gastrointestinal tract. Its deficiency and monoamine neurotransmitters are considered the main causes of depression. In the study of Chen Xiaojun [25] and others, it can be seen that lead exposure down-regulates the expressions of ChgA and TPH in the intestines of rats, further down-regulating the expressions of 5-HT and 5-HT3R, leading to depressive behavior. And qRT-PCR detection shows that the mRNA expressions of Lactobacillus and Bifidobacterium in the lead exposure group are significantly reduced, which is consistent with the results of flora sequencing. It indicates that the intestinal flora of rats in the lead exposure group is obviously disordered. Therefore, it is speculated that the intestinal flora may regulate the neurotransmitter 5-HT through the gut-brain axis and improve the depressive-like behavior caused by lead exposure, making more possibilities in the field of prevention and treatment of lead exposure neuropsychiatric diseases.

3. Conclusion

In conclusion, analyzing the mechanism of lead-induced neurotoxicity from multiple angles, many therapeutic targets for inhibiting toxic effects have been discovered one after another in recent years. Models are established for different research objects to study acute or chronic lead exposure, hoping to fill the gaps in the field of lead neurotoxicity mechanism research. In addition to the above mechanisms, some studies focus on changes in calcium homeostasis imbalance, apoptosis, autophagy, glial stress, and energy metabolism disorders. It can be mainly seen that the research is characterized by learning and memory disorders of nervous system diseases induced by lead, but also includes other mental diseases, such as depressive-like changes and anxiety-like changes. Signal pathways that induce oxidative stress are more common, and the occurrence of neuroinflammation may involve multiple pathways. Even if the above pathways are proven to be effective, currently these effects still cannot be completely attributed to the toxicity of lead and may be affected by confounding factors. In general, the mechanism of lead-induced neurotoxicity is multifaceted, but the exact mechanism has not yet been discovered. It still requires the joint efforts of researchers in this field and is committed to the coordinated development with the field of molecular biology. Providing new mitigation means for a further understanding of the mechanism of lead-induced neurotoxicity is crucial for developing new tools to alleviate and block the adverse effects of this metal on important parts.

References

[1] Wang Siyuan et al., A review of the sources and hazards of lead pollution in soil. Agriculture and Technology, 2022. 42 (09): pp. 78-81.

[2] Banna, H.U., et al., Parental Lead Exposure Promotes Neurobehavioral Disorders and Hepatic Dysfunction in Mouse Offspring. Biological trace element research, 2022. 200(3): p. 1171-1180.

[3] Gundacker, C., et al., Lead (Pb) and neurodevelopment: A review on exposure and biomarkers of effect (BDNF, HDL) and susceptibility. International journal of hygiene and environmental health, 2021. 238: p. 113855-113855.

[4] Yuanyuan, F., et al., Signal transduction associated with lead-induced neurological disorders: A review. Food and Chemical Toxicology, 2021. 150.

[5] Raheleh, R., et al., Hydrogen sulfide protects hippocampal CA1 neurons against lead mediated neuronal damage via reduction oxidative stress in male rats. Journal of Chemical Neuroanatomy, 2021. 112 (prepublish).

[6] Hua, Z.Z., et al., Maternal Lead Exposure Impairs Offspring Learning and Memory via Decreased GLUT4 Membrane Translocation. Frontiers in Cell and Developmental Biology, 2021. 9.

[7] Katherine A. Fitzgerald, D.C.R.B., LPS-TLR4 Signaling to IRF-3/7 and NF-κB Involves the Toll Adapters TRAM and TRIF. The Journal of Experimental Medicine, 2003. 198(7).

[8] Wang Weixuan et al., Injury mechanism of neuroinflammation in mice induced by lead and lipopolysaccharide exposure. Environmental and Occupational Medicine, 202.38 (07): pp. 763-768.

[9] Surjyadipta Bhattacharjee, Y.Z.P.D., I.R.W. Evgeny and J. Lukiw, microRNA-34a-Mediated Down-Regulation of the Microglial-Enriched Triggering Receptor and Phagocytosis-Sensor TREM2 in AgeRelated Macular Degeneration PLOS ONE, 2016.

[10] Bo Jianzhu, Study on the role of exosome miR-124/506 in lead exposure-induced neuroinflammation, 2021, North China University of Technology.

[11] Liu, J., et al., Microglia and astroglia: the role of neuroinflammation in lead toxicity and neuronal injury in the brain. Neuroimmunology and Neuroinflammation, 2015. 2(3).

[12] Ricardo, W., et al., Necroptosis in development, inflammation and disease. Nature reviews. Molecular cell biology, 2017. 18(2).

[13] A, V., Calcium and cell death. Sub-cellular biochemistry, 2007. 45.

[14] Manolis, P. and V. Peter, Necroptosis and its role in inflammation. Nature, 2015. 517(7534).

[15] Sudan, H., H. Song and S. Zhirong, Biomarkers for the detection of necroptosis. Cellular and molecular life sciences: CMLS, 2016. 73(11-12).

[16] Peng, S., et al., The role of NLRP3 in lead-induced neuroinflammation and possible underlying mechanism. Environmental Pollution, 2021. 287.

[17] YueSong, Z., et al., Sodium Para-aminosalicylic Acid Inhibits Lead-Induced Neuroinflammation in Brain Cortex of Rats by Modulating SIRT1/HMGB1/NF-κB Pathway. Neurochemical research, 2022.

[18] Mei, Y., et al., Dietary fiber ameliorates lead-induced gut microbiota disturbance and alleviates neuroinflammation. Journal of the science of food and agriculture, 2022. 102(15).

[19] Qixiao, Z., et al., Oral Supplementation of Lead-Intolerant Intestinal Microbes Protects Against Lead (Pb) Toxicity in Mice. Frontiers in microbiology, 2019. 10.

[20] Leilei, Y., et al., Dose-dependent effects of lead induced gut injuries: An in vitro and in vivo study. Chemosphere, 2021. 266.

[21] Breton, J., et al., Gut microbiota limits heavy metals burden caused by chronic oral exposure. Toxicology Letters, 2013. 222(2).

[22] Zhu Jiawei et al., Correlation between learning and memory changes and intestinal flora disorders in mice induced by lead exposure. Chinese Journal of Occupational Diseases in Occupational Health, 2022 (02): pp. 83-89.

[23] Yijing, C., et al., Gut Microbiome Alterations Precede Cerebral Amyloidosis and Microglial Pathology in a Mouse Model of Alzheimer's Disease. BioMed research international, 2020. 2020.

[24] Xiaozhen, G., et al., Probiotic Lactobacillus rhamnosus GR-1 supplementation attenuates Pb-induced learning and memory deficits by reshaping the gut microbiota&#13. Frontiers in Nutrition, 2022. 9.

[25] Xiaojun, C., et al., Role of 5-Hydroxytryptamine and Intestinal Flora on Depressive-Like Behavior Induced by Lead Exposure in Rats. BioMed Research International, 2021. 2021.

[26] Hoban, A.E., et al., Corrigendum to “Behavioural and neurochemical consequences of chronic gut microbiota depletion during adulthood in the rat” [Neuroscience 339 (2016) 463–477]. Neuroscience, 2017. 344.
[27] Alessandra, M., et al., Environment, dysbiosis, immunity and sex-specific susceptibility: a translational hypothesis for regressive autism pathogenesis. Nutritional neuroscience, 2015. 18(4).