Research Progress in Lead Neurotoxicity

Yumeng Li, Danni Huang, Liangrong Li, Rongna Rao, Yi Sun

School of Public Health, Guilin Medical College, Guilin, 541100,China.

Abstracts: Lead is a powerful toxic metal that can accumulate continuously along the food chain in the corresponding target organs of organisms through enrichment, thereby causing damage to the growth and development of the body. Current research generally believes that there is no threshold for the damage caused by lead to the human body, that is, any dose of lead may have harmful effects on the human body, so the neurotoxicity caused by lead exposure still receives widespread attention. This article summarizes the current situation of lead exposure, studies on different levels of lead neurotoxicity in humans, cells, and animals, and susceptibility markers, hoping to provide scientific basis for further research on lead neurotoxicity and formulating reasonable prevention and control measures in the future.

Keywords: Lead Exposure; Neurotoxicity; In Vitro and In Vivo Experiments; Gene Polymorphism

1. Introduction

As one of the most toxic and highest content elements in the earth's crust, lead can be inhaled, ingested, and exposed by humans through food, water, smoke, dust, soil, and skin. A large-scale cross-sectional retrospective study in the United States found that toxic metal lead can be detected in the blood of more than half of the tested children. Although the lead content of most children is relatively low, ranging from 1 to 2 ug/dl, about 2% of children still have relatively high lead content, which can reach 5 ug/dl or more [1]. This discovery not only illustrates the health problems in the United States, but also serves as a wake-up call for us. Therefore, this article reviews the current situation of lead exposure, studies on different levels of lead neurotoxicity in humans, cells, and animals, and susceptibility markers based on relevant literature in recent years, hoping to provide scientific basis for further research on lead neurotoxicity and formulating reasonable prevention and control measures in the future.

2. Lead exposure status

Lead, as a naturally occurring heavy metal, has been known for its low melting point, corrosion resistance, and resistance to X-rays and γ are used for advantages such as penetration and radiation. Studies have shown that the sources of lead exposure in Mexico include glazed ceramics, lead contaminated utensils, and lead contaminated water. The sources of lead exposure in France include lead paint from old houses, imported ceramics and cosmetics, and industrial emissions. The sources of lead exposure in Australia include paint, dust, imported toys, and traditional medicines. The sources of lead exposure in the United States include paint, industrial legacy lead exposure, and batteries. Finally, in China, The main sources of lead exposure come from electronic waste, traditional drugs, and industrial emissions [2]. Therefore, areas with dense heavy metal industries, large amounts of heavy metal pollutants per unit area, and severe deterioration of environmental quality are designated as heavy metal pollution areas, while areas without relevant polluting enterprises or with low background values for heavy metals are generally designated as areas.

2.1. Lead exposure in general areas

Lead in the environment mainly comes from two sources: one is natural sources, which refers to lead released into the environment by natural phenomena such as volcanic eruptions, flying ground dust particles, forest fire smoke, and sea salt aerosols; The second is caused by human activities, including the mining and smelting of lead and other heavy metal mines, the battery industry, the glass manufacturing industry, the production and use of pharmaceuticals, cosmetics, chemical reagents, and

【作者简介】李雨蒙（1997－），女（汉），桂林医学院公共卫生学院，硕士，研究方向为公共卫生。
【通信作者】孙易（1977－），女（汉），桂林医学院公共卫生学院，研究生导师，博士，研究方向为卫生毒理学。

other lead-containing products. About 95% of lead enters the human body from the digestive tract, so the detection of lead exposure in food is the focus of environmental monitoring in general areas. The study of lead pollution in 24 types of common vegetables in Haishu District of Ningbo showed that the detection rate of heavy metal lead in all vegetables was 25.20% (detection limit: 0.02 mg/kg), the total single factor pollution index of Pb in vegetables was 0.18, and the single factor pollution index of Pb in 24 types of vegetables was 0.04-0.41, all<0.7, indicating that the pollution level of heavy metal Pb content in locally grown common vegetables in Haishu District of Ningbo City was evaluated as excellent. However, there is a phenomenon that the content of heavy metals in individual samples exceeds the standard [3]. A study based on Wuhan adult population shows that there is a relationship between lead in urine and diabetes, although the author emphasizes that more studies are needed to further confirm this relationship.

2.2. Lead exposure in heavy metal contaminated areas

Industrial pollution such as coal emissions and metal smelting is the largest and most frequent source of lead pollution, accounting for 63.7% to 76.7% of the total. Therefore, heavy metal pollution areas are often located near such operations. The situation of lead pollution in the soil around typical mining areas in northern Guangxi indicates that the lead content in edible parts of crops such as peanuts and pakchoi in the study area exceeds the threshold value specified in the national food safety standard (GB2762-2017), posing a high health risk. In the study of food lead pollution in Shaanxi Province, it was detected that the lead content exceeded the standard by 2.18%, with an average of 0.0461 mg/kg. The average weekly lead intake by Shaanxi residents through food was 4.45 ug/(kg · BW), accounting for 17.80% of the original PTWI, indicating that there is a certain degree of lead pollution in food in Shaanxi Province, which can cause certain health risks.

3. Study on lead neurotoxicity in different populations of children and adults

Lead exposure can cause health problems for all humans. In 2021, the United States Centers for Disease Control and Prevention (CDC) announced that public health action should be taken immediately when the reference value for blood lead in young children is 3.5 μ g/dl, while recognizing that although it is useful as a risk management tool, a blood lead level of 3.5 μ g/dl should not be interpreted as a toxicity threshold. In fact, no threshold has been determined yet.

3.1. Effect of lead on cognitive function in children

Children are at higher risk of lead exposure than adults because they are more likely to play in dirt, absorb about half the oral dose of water-soluble lead into the body by putting hands and other objects into their mouth, and are most likely to experience adverse effects due to rapid growth and neurodevelopment during this period. Some studies say that the blood lead level of children aged 0-6 years in China is correlated with age, and it can show a trend of increase with the growth of age. The blood lead concentration in the 1-year-old group is 6.29 u g/dl as the lowest, and the blood lead concentration in the 6-year-old group ranks first with 9.16 u g/dl. Blood lead levels in children around the lead-zinc mining area were relatively high and had regional, sex and age distribution differences. Correlation analysis showed that children's emotional symptoms, conduct problems, inattention, peer problems and total difficulties were all positively correlated with blood lead levels . There was a significant negative correlation between lead exposure dose and duration and cognitive function test scores.Many studies have clarified the impact of lead on childhood developmental outcomes, leading more susceptible to CNS effects in the critical developmental window compared to adults. The correlation between maternal blood lead and cord blood lead levels confirms that lead can be transferred from the mother through the placental barrier to the fetus. The earliest score from the Bailey Infant Development Scale (BSID) showed that high cord blood levels were associated with lower covariance adjustment scores on the mental development index (MDI). In a prospective longitudinal cohort study of 362 children from birth to three, liu et al evaluated the relationship between prenatal and postnatal exposure to low levels of lead and early cognitive development, found that prenatal and postnatal lead exposure as low as 5 μ g/dl can adversely affect neurodevelopment, and the observed trend of cognitive deficits starting from 6 months of life may persist, even in the next few years.

3.2. Effects of lead on adult cognitive function

Lead has long been recognized as a developmental neurotoxicant. Long-term lead exposure in adults can cause changes in the nervous system, such as slow nerve conduction, fatigue, mood swings, drowsiness, inattention, headache, coma, etc., and even potential risk factors for neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. With the continuous formulation and implementation of lead control policies in recent years, the level of lead exposure in the environment has been greatly reduced, and adults with frequent contact with lead are more common in occupational groups. In the blood lead physical examination of the workers in a battery factory in a city, the blood lead concentration of the exposed group was between 56.3 and 429.8 μ g / dl, and the blood lead level of the lead workers showed an increasing trend with the increase of age.A cohort of a large number of current and former inorganic lead workers found associated with subclinical neurocognitive deficits when blood lead concentrations were in the range of about 20 – 50 μ g / dl, while in a cross-sectional analysis of 107 occupational-exposed individuals showed an increased in the incidence of depression, confusion, anger, fatigue, and tension in patients with plasma concentrations> 40 μ g/ dl. It is reported that in the neuropsychological test of lead battery factory workers, the average blood lead level of the experimental group was 3 times that of the control group, and there was a correlation between tibial lead content and cognitive function, mainly showing that the behavioral performance ability of the experimental group during the follow-up compared with the control grou.*[4]* In addition, a case-control study found that the mean blood lead concentration in Alzheimer's patients was 22.22mg/dL, significantly higher than the control, suggesting that the level of lead exposure is closely related with Alzheimer's disease.

4. In vivo experimental study of lead neurotoxicity

Neurotoxicity caused by lead exposure is mainly manifested in learning disabilities and behavioral abnormalities. Mice exposed to lead can experience memory impairment, distraction, and delayed spatial cognitive flexibility. In addition to cognitive impairment, the changes in exercise effects in mice exposed to lead were also significant. Studies have shown that exposure to lead during pregnancy and lactation can lead to neurobehavioral defects that can persist into adulthood. Placing the offspring of weaned rats in a poor or fertile environment can be observed that the performance of lead exposed rats reared in a fertile environment is similar to that of the control group animals not exposed to lead, while the spatial ability of lead exposed animals reared in a poor environment decreases relative to the control group rats in the Morris water maze [5].

5. Experimental study of lead neurotoxicity in vitro

The objective of in vitro experimental studies of lead neurotoxicity is to identify the molecular and cellular changes that lead to behavioral defects, and to determine the mechanisms of lead uptake and tolerance in lead accumulating cells.

Li Zhaocong found that compared with the control group, the lead exposed group exhibited nuclear fragmentation in hippocampal neurons, with an increased rate of early and late apoptosis. He speculated that lead might induce neuronal apoptosis through the IP3R-Ca2+- p38 signaling pathway. Oligodendrocytes are another type of glial cells that are mainly responsible for producing and maintaining the protective myelin sheath of insulating axons. Lead can disrupt the development and maturation of oligodendrocytes by interfering with galactolipid metabolism enzymes, leading to neurotoxicity [6]. In addition, low concentrations of lead can compete with Ca2+for binding sites on calmodulin independent protein kinase C, thereby affecting neuronal signal transduction and neurotransmitter release.

6. Susceptibility markers of lead neurotoxicity

The neurotoxicity caused by lead exposure can lead to a variety of adverse outcomes for the central nervous system. In addition to adverse effects on young people, lead accumulated throughout life can also have negative cognitive consequences for older people, such as Alzheimer's disease (AD) and Parkinson's disease (PD). However, there are differences in individual susceptibility, and one possible explanation is genetic susceptibility, such as δ- Polymorphisms in the aminolevulinate dehydratase

(ALAD) gene, 5-hydroxymethylcytosine (5-hmC), and SNCA genes can be used as predictive markers to prevent neurotoxicity caused by lead exposure.

SNP variants of the SNCA gene may determine the risk of lead induced PD. Specifically, lead only increases the probability of PD in subjects carrying non harmful SNCA alleles, while subjects with highly sensitive SNCA alleles are less affected [7]. In addition, intracerebral cavernous hemangioma 3 (CCM3) is highly expressed in neurovascular units. Some studies have suggested that when it mutates, it may induce apoptosis, thereby affecting the stability of vascular endothelial cells, altering vascular permeability, and causing neurotoxicity. It is speculated that during occupational lead exposure, the CCM3 gene polymorphism may be related to the load of lead in the body and the susceptibility to chronic poisoning. Although relevant experimental research results at the molecular level suggest that CCM3 gene polymorphism may affect lead absorption into the bloodstream, relevant evidence has not been found in the population epidemiology study conducted by Liu Qingxiang [8], and the impact of CCM3 gene polymorphism remains to be further explored.

7. Conclusion

At present, domestic research on the molecular mechanism of lead neurotoxicity still needs to be further deepened. Neurotoxicity caused by lead exposure remains an important public health issue, as they pose a serious threat to human health and even life. We should strive to improve environmental safety, continuously expand our knowledge of the field of toxic element pollution, including lead, enhance people's self-protection awareness, and optimize measures to protect vulnerable populations to promote and achieve common health.

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