Molecular toxicological mechanisms and Health Risks of Mercury: Environmental Exposure, Biological Effects and Control Strategies

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Abstract. Mercury (Hg), a global heavy metal pollutant, poses a serious threat to ecosystems and human health due to its persistence, bioaccumulation and high toxicity. This paper systematically reviews the environmental distribution, exposure routes, molecular toxicological mechanisms and health risks of mercury. Mercury forms a complex network of pollution through atmospheric transport, water circulation and soil accumulation, with the food chain being the main route of human exposure. Molecular mechanism studies have shown that mercury binds to selenocysteine residues in the thioredoxin system (Trx/TrxR) and disrupts the pentose phosphate pathway (PPP), resulting in insufficient NADPH production, reactive oxygen species (ROS) accumulation and mitochondrial damage. At the same time, mercury interferes with glutamate homeostasis, triggering neuronal excitotoxicity and exacerbating neurodegenerative disorders. Epidemiological evidence shows that mercury exposure is closely associated with elevated levels of autoantibodies in the brain of autistic individuals, abnormal social behavior in offspring, and an increased risk of cardiovascular disease, and the resulting mutations can persist across generations. Current mercury pollution control technologies can effectively reduce pollution, but they have limitations such as secondary pollution and long cycles. In the future, the focus should be on developing efficient and environmentally friendly control strategies and strictly implementing the Minamata Convention to control emissions from the source. This paper provides a scientific basis and theoretical support for the global governance of mercury pollution and the protection of human health.

Keywords: Mercury toxicity, environmental exposure, toxicity mechanism, pollution remediation.

1. Introduction

Mercury (Hg) is a heavy metal toxicant that is widely present in the environment and medical products and poses a serious threat to ecosystems and human health due to its persistence, bioaccumulation, and high toxicity. Despite several control measures taken by the international community; the problem of mercury pollution remains far from optimistic. Mercury and its compounds can enter the human body through food chains, vaccine preservatives (such as thiomersal), etc. The total daily dietary mercury intake estimated by different food types among Zhoushan residents indicates that fish intake is the main source of mercury exposure [1]. Mercury and its compounds can cause damage to the central nervous system, kidneys and immune system. For example, there is a link between mercury exposure and autoantibodies in the brain of individuals diagnosed with autism, and the levels of these antibodies in the brain have a certain impact on the severity of autism [2]. Recent studies have also shown that the toxicity of mercury is closely related to its disruption of cellular antioxidant systems and energy metabolism pathways. Among them, the Thioredoxin System (Trx/TrxR) and the Pentose Phosphate Pathway (PPP) are core targets [3].

Based on the environmental distribution, exposure routes, molecular toxicology and epidemiological evidence of mercury, this paper explains the distribution of mercury pollution, the mechanism of its toxic effects and the combined impact on health and evaluates the advantages and limitations of current mercury pollution control technologies, providing a scientific basis for the optimization of mercury pollution control strategies and the protection of population health. It provides theoretical support for global environmental governance of mercury and public health decision-making.

2. Environmental distribution and exposure routes of mercury

Mercury, as a highly toxic global pollutant, its environmental distribution and impact on human health have become major global concerns. The distribution of mercury in the environment has significant spatial and medium heterogeneity, forming complex pollution networks mainly through atmospheric transport, water circulation and soil accumulation, and it has neurotoxicity, cardiovascular toxicity, etc. to humans [4]. Take the mining ecosystem in China as an example. As an important region for the distribution and exploitation of mercury resources globally, environmental mercury pollution and human exposure risks in mercury mining areas are particularly prominent in China. Feng Xinbin et al. 's research on China's mercury mining areas shows that mercury mining activities have led to significant increases in mercury concentrations in the atmosphere, water, soil and biological media of the mining areas. Among them, the mercury concentration in the atmosphere can reach 7.4-1950 ng/m3, the mercury content in the soil can reach up to 790 mg/kg, and the methylmercury content in the paddy field soil is significantly higher than that in the control area [5]. Population exposure assessment showed that the daily exposure of methylmercury ingested by the residents of the mining area through rice was up to 1.9 μg/kg, with a risk factor of 8.1. Although the average exposure through a single route did not exceed the international safety limit, the combined exposure risk factor of inorganic mercury and methylmercury exceeded 1.0, indicating that sensitive populations (such as pregnant women and infants) faced potential health threats. The study further pointed out that the accumulation of methylmercury in rice, which is the staple food for the residents of the mining area, is closely related to the microbial methylation process in the paddy field wetland ecosystem. Sulfate-reducing bacteria activity and seasonal waterlogging conditions significantly promote mercury methylation, forming a "soil-rice" enrichment pathway.

Mercury pollution is a key concern in China's mining areas and a major challenge to global environmental governance. In the future, a comprehensive study of typical cases worldwide will be needed, and the application of cutting-edge technologies such as mercury isotope tracing and microbial regulation will be deepened to provide a scientific basis for mercury pollution control and human health protection.

3. Molecular toxicity mechanism of mercury

3.1. Mechanisms of mercury toxicity to Trx and ppp pathways

The thioredoxin system, consisting of Trx and TrxR, relies on NADPH to maintain cellular REDOX balance and is the core of antioxidant defense. Its main functions include eliminating free radicals (such as reactive oxygen species (ROS)) and repairing oxidized damaged proteins; It regulates REDOX signaling and participates in cell proliferation, apoptosis and DNA synthesis, etc. The experiment measured thioredoxin reductase (TrxR) activity using purified enzyme insulin reduction method and found that EtHg and methylmercury (MeHg) had significant inhibitory effects on purified TrxR, with half maximal inhibitory concentrations (IC50) of 96.1nM and 105.8nM, respectively. TM was less toxic (IC50=144.3 nM) [3]. The principle is that as an electrophilic reagent, mercury, upon entering the cell, immediately binds to the -SeH group on the selenocysteine residue at the active center of TrxR, blocking its catalytic function and thereby affecting the activity of TrxR. In addition, mercury binds to the thiol group (-SH) in proteins, causing enzyme inactivation and protein denaturation.

PPP is a key metabolic pathway in cells that generates NADPH and ribose-5-phosphate, divided into oxidizing and non-oxidizing phases. The oxidative phase is catalyzed by glucose-6-phosphate dehydrogenase (G6PDH) and 6-phosphogluconate dehydrogenase (6PGDH) to produce NADPH and ribose-5-phosphate. Among them, NADPH has the function of maintaining the reduced state of the thioredoxin system (Trx/TrxR) and the glutathione system (GSH), eliminating free radicals and protecting cells from oxidative damage. All mercury compounds significantly inhibited the activity of G6PDH and 6PGDH and induced excessive production of reactive oxygen species (ROS) [3]. This

leads to insufficient NADPH production, ultimately causing the Trx system to fail to function, and the accumulation of free radicals exacerbates mitochondrial damage. In addition, this leads to a reduction in ribose-5-phosphate, which affects RNA and DNA synthesis and hinders cell proliferation and repair.

3.2. Other toxic mechanisms of mercury

In addition to causing oxidative stress in cells and leading to mitochondrial dysfunction, mercury also causes dyshomeostasis of glutamate in the body [6]. As the main excitatory neurotransmitter in the central nervous system, the dynamic balance of glutamate is crucial for the normal functioning of neurons. Mercury and its compounds can cause abnormal glutamate signaling by interfering with the release and uptake of glutamate, resulting in excitotoxicity of neurons, a process of neuronal death caused by the excessive and persistent activation of excitoneurotransmitters - glutamate receptors [7]. This is one of the core mechanisms of its neurotoxicity. Mercury compounds significantly suppress the ability of astrocytes to reuptake glutamate in the synaptic clem by targeting glutamate transporters. Experiments have shown that methylmercury can block the active transport of glutamate by astrocytes, resulting in an abnormally high concentration of glutamate in the synaptic cleft [8]. This dual effect of inhibiting uptake and promoting release disrupts the dynamic balance of glutamate, causing sustained neuronal activation and significant damage to the body. The increase in glutamate concentration also causes the NMDA receptor to be overactivated, leading to a large influx of calcium ions [7]. High intracellular concentrations of Ca^{2+} can lead to the overactivation of some enzymes and trigger some calcium ion-dependent protein-protein reactions, ultimately causing the destruction of multiple organelles, disrupting cell homeostasis and resulting in cell death.

4. Health effects and epidemiology

4.1. Neurotoxic effects

It is well known that there are many kinds of neurotoxic effects of mercury. However, the immunological changes in the brain caused by mercury exposure are less known. But its neurotoxic effects are of equal importance. It is mainly characterized by disorders of autoimmune function, including the production of highly specific brain autoantibodies. Kern et al. examined all papers that provided relevant information between 1985 and 2020 [2]. They found autoantibodies against brain tissue in children diagnosed with autism. Moreover, these antibodies seem to be associated with the severity of autism. There is also evidence that mercury levels in the blood can affect the levels of these autoantibodies. Zhang et al. investigated the long-term effects of maternal exposure to mercury chloride during pregnancy and lactation on the immune system and social behavior of offspring and explored the mechanism of neuroinflammation in this process [9]. They exposed the experimental group of female mice to mercury and observed the immune indicators, brain pathology and behavioral changes of the offspring. It was found that the social behavior of the offspring was significantly impaired, and the female offspring were more severely impaired than the male offspring. This study reveals the complex mechanisms by which mercury exposure during development affects the social behavior of offspring and also indicates that the neurotoxicity of mercury can not only cause direct damage to cells but also interfere with neurodevelopment through indirect pathways that affect antibody levels in offspring.

4.2. Cardiovascular toxicity

Mercury has an extremely strong binding ability to sulfhydryl groups, which causes mercury to affect the activity of many enzymes, thereby inhibiting many enzymatic reactions. Mercury can also cause oxidative stress and mitochondrial dysfunction in the body, thereby damaging the cardiovascular system. Houston systematically reviewed the toxic effects of mercury and its association with cardiovascular diseases such as hypertension and coronary heart disease [10]. Research mentioned that mercury can increase the aggregation of clotting factors and platelets,

thereby promoting thrombosis; It also indirectly aggravates hypertension by suppressing the function of immune cells and causing kidney damage. Fortunately, selenium can reduce its toxicity by forming selenium-mercury complexes, while fish intake increases mercury exposure, but its omega-3 fatty acids still protect the cardiovascular system.

4.3. Reproductive toxicity

In addition to damage to the nervous and cardiovascular systems, mercury also has some negative effects on the reproductive system. Studies have found that methylmercury has a significant effect on epigenetic mutations in zebrafish sperm [11]. Direct exposure of the F0 generation to methylmercury led to the production of 291 differentially methylated regions in sperm. Most of these associated genes are involved in the translation process and may have some connection with the regulation of early development. The differentially methylated regions in F2 generation sperm increased significantly and were more widely distributed. These mutations can persist across generations and eventually lead to neurobehavioral abnormalities in the offspring. To investigate the effects of mercury on the maturation and fertilization ability of mouse oocytes, Shen et al. used in vitro oocyte culture and in vitro fertilization [12]. The results showed that high doses (1.5 mg/kg BW) of mercury chloride significantly reduced the number of superovulation oocytes and decreased ovarian activity. Mercury chloride inhibits the release of the first polar body from the oocytes used in the experiment, stopping the meiotic process and preventing it from entering the second meiotic process, thereby increasing the mortality rate of oocytes and affecting normal fertilization of oocytes.

5. Treatment methods for mercury contamination

Mercury is highly toxic, persistent and bioaccumulative, and mercury pollution is growing worldwide today. As a result, the management of mercury pollution has become a key and difficult point in soil pollution control. The current remediation techniques for mercury-contaminated soil mainly fall into two categories: physicochemical remediation and biological remediation. The main methods include leaching, solidification and biological remediation, etc. [13]. Leaching mainly separates mercury from the soil through physical separation or chemical extraction and is suitable for low organic matter, sandy or silty soil. It has the advantages of a short processing cycle and mercury recovery, but it is less effective on clay or humus-rich soil and is prone to secondary pollution and damage to soil structure. The solidification rule is through chemical stabilization, such as adding sulfides to the soil to fix Hg to form HgS; Or physical encapsulation, such as by chemically bonding phosphate ceramic techniques to reduce mercury mobility and concentration in the soil. This method is more thorough in dealing with pollution, but it also has limitations such as increased volume after solidification and damage to soil fertility. Bioremediation takes advantage of the fact that some organisms accumulate mercury to reduce the mercury content in the soil. The greatest advantage of this method is that it is environmentally friendly and low-cost. But it has a long repair cycle and cannot reduce the impact of mercury pollution in a short time. And the treatment of the enriched organisms is also a problem. Overall, research on mercury pollution control is quite mature.

6. Conclusion

Mercury, as a global pollutant, has a wide range of environmental distribution and diverse exposure routes. Especially in pollution hotspots such as mercury mining areas, it poses a significant threat to human health through a complex network of pollution formed by the atmosphere, water bodies and soil. Although there has been a lot of research on mercury around the world, there are still many unknown areas that need further exploration. Studies have shown that fish and rice are the main sources of mercury intake, and people living in mining areas are exposed to mercury pollution for a long time, and some groups, such as pregnant women and infants, are at potential health risks. Mercury can cause oxidative stress, mitochondrial dysfunction and glutamate homeostasis imbalance,

which in turn can lead to neuroexcitotoxicity, cardiovascular damage and reproductive system abnormalities.

In terms of pollution control, existing physical and chemical remediation techniques can quickly reduce mercury concentration, but they have problems of secondary pollution and damage to soil structure; Although bioremediation is environmentally friendly, it takes a long time and the treatment of enriched organisms is rather troublesome. Therefore, in the future, advanced technologies such as mercury isotope tracer will be needed to develop efficient, economical and environmentally friendly treatment strategies. It is also necessary to strictly adhere to the provisions of the Minamata Treaty, strictly control mercury emissions, and reduce mercury pollution at the source.

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