The Neurotoxicity Effect and Molecular Mechanism of Fine Particulate Expose-Induced Nervous System Injury

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Abstract: The potential harm of atmospheric fine particulate matter to human health has been widely concerned around the world. A growing number of studies have shown that PMs exposure can cause damage to respiratory and cardiovascular systems. However, whether PMs can enter the brain and produce neurotoxicity has been an important research topic in the field of neurotoxicity and public health hazards in recent years. In this paper, we review the existing epidemiological evidence and related experimental results to discuss the potential pathways and mechanisms of neurotoxicological effects of PMs on brain. It has been reported that atmospheric PMs can affect the nervous system through the olfactory nerve pathway, blood circulation and other pathways, causing oxidative stress, glial cell activation, neuroinflammation, synaptic plasticity changes and organelle damage and other neurotoxicity. On this basis, it is pointed out that future research in this field should be carried out by multidisciplinary experts in atmospheric chemistry, toxicology and epidemiology.

1 INTRODUCTION

In recent decades, air pollution and health risks caused by human activities have become an important issue of global concern. Air pollutants are a complex mixture of atmospheric particulate matter (PMs), organic components, metals, and gases (such as nitrogen oxides, sulfur oxides, and ozone). Among them, PMs is one of the most ubiquitous air pollutants. It is a complex, ever-changing particulate matter suspended in the air, varying in size and composition. Fine particulate matter is defined as particles with an aerodynamic equivalent diameter of 2.5μm or less, also known as $PM_{2.5}$, which is composed of primary particles directly discharged into the air and secondary particles generated by chemical transformation of gaseous pollutants (Jiang 2020).

As particle size is relatively small and suspended in the air for a long time, $PM_{2.5}$ will enter the body through the nasal cavity or mouth with the air, and negatively affect human health. Due to different particle sizes, particulate matter will deposit and stay in different parts of respiratory tract after entering the human body, resulting in a variety of respiratory diseases (Kang 2020). Details of deposition are shown in Figure 1.

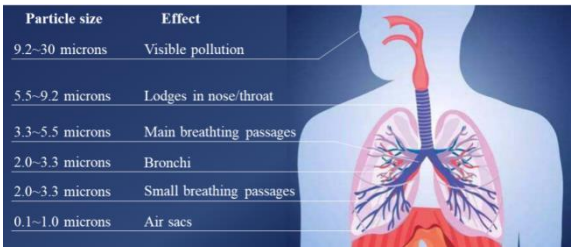

Figure 1: Location of particulate matter deposition in human respiratory tract

At present, studies on the impact of particulate matter on human health are mainly carried out from the size and surface of particulate matter, as well as the number and composition of particulate matter. Li Ben processed $PM_{2.5}$ extract by ultrasound and dispersed it evenly in neural culture medium. The morphological characteristics of SEM and TEM are shown in Figure 2 (Li 2018). $PM_{2.5}$ is composed of various components, which can absorb and transfer a large number of harmful substances. Its main components include biological sources, ions, organic compounds, metal ions and carbon particles. Research has shown that ultrafine particles and fine particulate matter in the aspect of mortality, cardiovascular and respiratory diseases than large particles are more dangerous, because the particles on the adhesion of the composition such as persistent organic pollutants, heavy metals can be fine particles reach the alveoli, the alveolar structure of epidermal cells into the blood, through the circulation of the blood other target organ damage. A growing number of studies have shown

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that fine particulate matter exposure will cause damage to the nervous system, and the brain is a potential target organ of $PM_{2.5}$(Fagundes 2015).

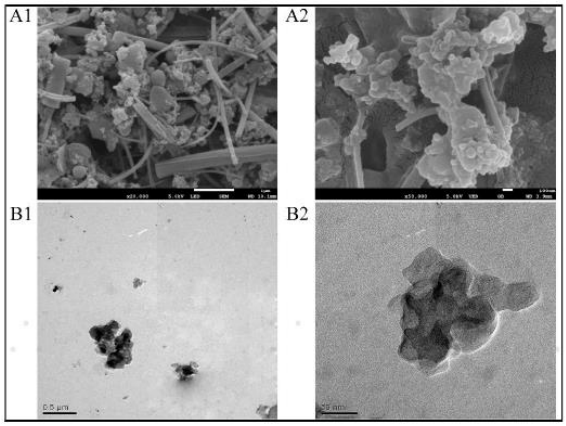

Figure 2: Morphological characteristics of $PM_{2.5}$

2 $PM_{2.5}$ AND NERVOUS SYSTEM DAMAGE

Further laboratory studies have found that when inhaled through the nose, most of the fine particles are removed by mucosal fibers in the lungs or eaten by macrophages. However, a small part of particulate matter will escape the reticuloendothelial surveillance system and deposit in the lung system, and then enter the systemic circulation through alveoli-capillaries, and then induce nervous system damage in two ways. (I) Particles stimulate the lung system, triggering local and systemic inflammation, and these inflammatory mediators or cytokines can penetrate into the systemic circulation and act on the nervous system. (II) Some specific nanoparticles may escape the reticuloendothelial system and directly stimulate the blood-brain barrier (BBB) with blood circulation, resulting in changes in BBB membrane permeability and subsequent brain injury. As shown in figure 3 (Mutlu 2018), in addition, the nasal cavity and eyes are also one of the exposure methods of $PM_{2.5}$. Particles passing through the nasal cavity can enter the blood circulation through the epithelial barrier or migrate to the olfactory nerve axis and burst into the central nervous system (CNS) (Ajmani 2016). Epidemiological investigations have shown that long-term exposure to $PM_{2.5}$ increases the risk of ischemic stroke disease, Alzheimer's disease (AD), Parkinson's disease (PD) and other neurodegenerative diseases in middle-aged and elderly people (Flores-Pajot 2016.). In addition, prenatal and postnatal exposure to $PM_{2.5}$ may impair neurodevelopment and clinical cognitive behavior in early childhood, adolescence and adulthood (Lilian 2016). Due to the influence of exposure mode, composition, age and physical condition of exposed population, the mechanism of $PM_{2.5}$ induced nervous system injury is also elusive. Currently, confirmed mechanisms include oxidative stress, glial cell activation, nerve inflammatory, synaptic plasticity change and organelle injury.

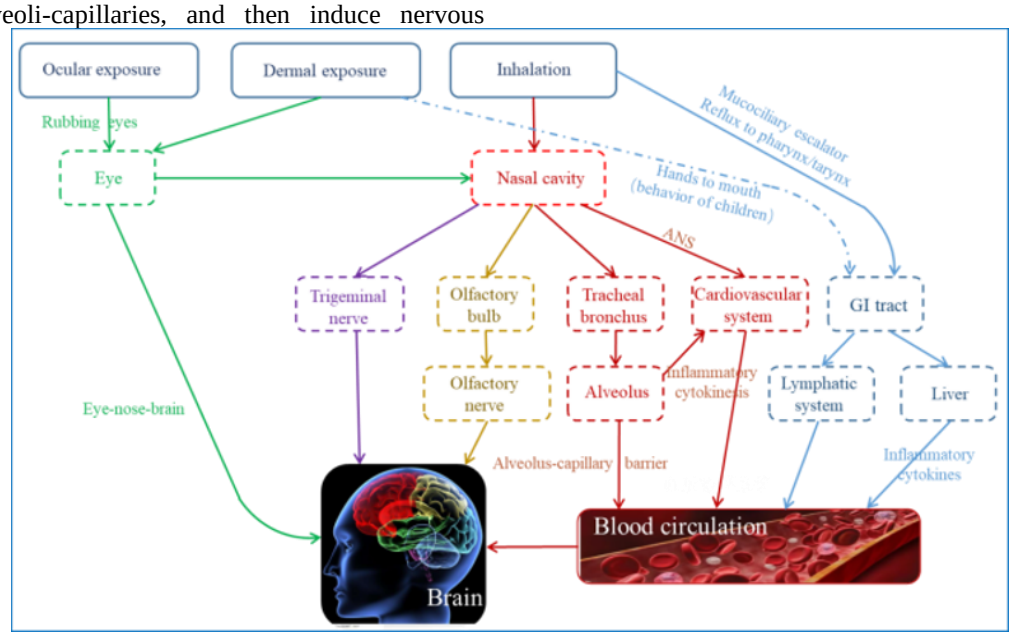

Figure 3: $PM_{2.5}$ induces central nervous system toxicity through different pathways

2.1 Oxidative stress

During the formation process, $PM_{2.5}$ will absorb many redox components, such as transition metal, quinone in automobile exhaust, cigarette smoke and secondary organic aerosol (SOA), etc. (Verma 2015.). When inhaled and deposited in the human respiratory tract, they continue to produce reactive oxygen species (ROS) in different ways. Electrons from the first transfer to the transition metal ions or quinone antioxidants, respectively form reduction of the state of the metal ions or half quinone (Uirich 2015), metal ions in the body and half quinone oxidation by O_2 again, O_2-free radicals, O_2-free radicals were further converted to hydrogen peroxide, which is the center of the respiratory tract free radicals reaction cycle and oxidative stress (Winterbourn 2015). Iron or copper ions can generate OH free radicals through Fenton reaction (Charrier 2011), while SOA can directly

release OH free radicals through interaction with water (Tong 2016). In addition, the substances carried by $PM_{2.5}$ can produce oxidative stress. After some PMs enters the blood circulation, protein corona is formed on the particle surface due to the interaction of protein electrostatic, hydrophobic bond and hydrogen bond. Protein halos change the size, absorption, translocation and elimination of nanoparticles, and then interact with cells to generate free radicals, leading to peroxidation damage of lipids, proteins and nucleic acids (Wang 2017).

2.2 Induce nerve inflammatory

Inflammatory response is a common self-defense response, but it can also cause different degrees of self-injury. Earlier studies have looked at the brain as an immune-privileged organ because of the BBB. But a growing number of epidemiological studies have found that after long-term exposure to relatively high concentrations of $PM_{2.5}$, children, adults and the elderly inevitably appeared inflammatory reaction in the brain nerve, and may promote neurodegenerative diseases such as the stroke, AD, PD and multiple sclerosis (MS), and even develop into depression, suicide and other neuropsychological diseases (Roberto 2018, Lilian 2015). The study found that $PM_{2.5}$ may trigger CNS inflammation through two pathways. (I) It can trigger neuroinflammation through systemic inflammation. $PM_{2.5}$ first induces the inflammatory response of the cardiopulmonary system and promotes the release of inflammatory factors, which reach the cerebrovascular system from the cardiopulmonary system and destroy BBB and induce the inflammation of the nervous system (Dantzer 2008). (II) Due to the large specific surface area, ultrafine particles of $PM_{2.5}$ can easily pass through the cell membrane, cross the BBB and reach the brain parenchyma, or directly enter the brain tissue through the olfactory bulb-entorhinal cortex and induce neuroinflammation.

2.3 Glial cell activation

With the occurrence of neuroinflammation, the levels of astrocyte activation marker glial fibrillary acidic protein (GFAP) and microglial activation marker CD14 were significantly increased after $PM_{2.5}$ entry (Kleinman 2008). Microglia, a type of glial cell that corresponds to macrophages in the brain and spinal cord, are the first and most important immune line in the CNS. Normally, microglia are constantly clearing damaged nerves, plaques, and infectious substances from the CNS. However, over-activated or out-of-control microglias will greatly enhance inflammatory responses, change synaptic structural functions and even aggravate neuronal death, and these adverse reactions will in turn stimulate further activation of microglias and neuronal death, which is a chronic vicious cycle that seriously harms CNS. Astrocytes play an important role in stabilizing ions, neurotransmitters, neurotrophic secretory factors and maintaining BBB integrity. Once the nervous system is damaged, astrocytes are immediately activated, and the activated astrocytes become hypertrophic, increasing the production of GFAP, forming a glial scar and blocking axon regeneration. Therefore, glial cell activation and neuroinflammation may act on nerve cells together to promote $PM_{2.5}$-induced nervous system damage.

2.4 Synaptic plasticity change

The unerring transmission of information between neurons is the basis of brain activity. Chemical synapses, which are composed of presynaptic membrane, synaptic cleft and postsynaptic membrane, are the main means of CNS signal transmission. When the nerve impulse is transmitted from the nerve fiber to the terminal, the presynaptic membrane generates an action potential, causing depolarization, activating the voltage-gated Ca^{2+} channel in the presynaptic membrane, allowing extracellular Ca^{2+} to enter the nerve terminal, and inducing synaptic vesicles containing neurotransmitters to fuse with the presynaptic membrane, releasing neurotransmitters. During synaptic transmission, intracellular calcium concentration, synaptic vesicle proteins, synaptic membrane proteins, neurotransmitters, ion channel receptors and so on can directly or indirectly affect this process. A growing number of studies have found that $PM_{2.5}$ exposure induces changes in synaptic structure and function. For example, Liu found that $PM_{2.5}$ induces macrophages and microglias to release the excitatory neurotransmitter glutamate, and glutamate may stimulate neuronal synapses and induce excitatory toxicity (Liu 2015). Ku's study found that the expression levels of NMDA and AMPA receptor subunits (GluA1, GluA2, GluN1, GRIN2A, GRIN2B) in hippocampal tissues decreased after long-term exposure to urban $PM_{2.5}$, and LTP in hippocampal brain slices decreased. The studies suggest that $PM_{2.5}$ may affect synaptic plasticity and induce nervous system injury through Ca^{2+} concentration, neurotransmitters, synaptic proteins or ion channel receptors.

2.5 Organelle injury

$PM_{2.5}$ stimulation can produce excessive cytokines and ROS, which greatly interferes with the homeostasis of intracellular organelles, such as mitochondria. Mitochondria are sensitive organelles to oxidative damage and homeostasis. Mitochondrial damage not only affects the production of ATP, but also participates in oxidative stress, apoptosis, autophagy and other life activities. The brain is an organ with high energy consumption, and mitochondrial damage may cause more serious harm, and even participate in PM-induced nervous system damage. Fuller's study found that rats exposed to environmental tobacco smoke after delivery had cerebellar mitochondrial proteomic disturbances, heterotopic mitochondrial membrane hexglycosylase (Hk1), and increased expression of ATP synthase and mitochondrial fission factor engine-like protein 1 (Dnm1l). The abnormalities may be associated with known cerebellar developmental disorders and diseases induced by environmental tobacco smoke exposure.

Moreover, cigarette smoke may directly affect mitochondrial enzyme activity and cause brain toxicity. In addition to mitochondria, endoplasmic reticulum and lysosome may also be targets of $PM_{2.5}$ action. Under normal physiological conditions, moderate ER stress can protect cell activity, while excessive ER stress can trigger cell apoptosis, which is the third apoptotic signaling pathway different from death receptor and mitochondrial receptor pathways (Rao 2004).

It is worth noting that $PM_{2.5}$ damage to the nervous system may be affected by age, sex, genotype and lifestyle. Growth, development, maturity and aging are the state that the brain must go through. In this process, growth, development and aging are more sensitive to external stimuli, and the same infants and the elderly are more likely to be affected by $PM_{2.5}$ after exposure, exacerbating neurotoxic effects. And, aging itself can age the immune system, exacerbating the accumulation of neuroinflammation in the brain of the elderly and promoting the development of neurodegenerative diseases. Exposure to airborne PM in early childhood accelerated brain aging and accumulation of amyloid beta 42 (Aβ42) and alpha-synuclein. In addition to age, genotype is also an important factor. Epidemiological investigations and experimental studies have found that people with apolipoprotein E (ApoE) 4 allele are more susceptible to air pollution, and the ApoE4 allele is recognized as the most common genetic risk for AD (Lilian 2016). In addition, mitochondrial DNA haplotype may change individuals' susceptibility to particle cognitive effects (Colicino 2014). Although more and more data are revealing the relationship between $PM_{2.5}$ and neurodegenerative diseases, further research is needed on initiating molecular events and key toxic pathways.

3 CONCLUSIONS

The origin and genesis of PMs are complex, and the composition of PMs varies greatly in different seasons and regions. Multiple omics studies of PMs and its specific components are helpful to comprehensively elucidate the neurotoxicological mechanism of atmospheric particulate matter. The damage caused by atmospheric particles to a system is not isolated. Establishing a system of in vitro co-culture of nerve cells will be the trend of studying the neurotoxicological effects and mechanism of PMs in the future. Therefore, it is suggested that future research on atmospheric particulate matter should be carried out by multidisciplinary experts in atmospheric chemistry, toxicology and epidemiology.

Traffic emission is one of the important sources of urban particulate matter. In recent years, Chinese government has vigorously encouraged the production and use of new energy vehicles, and the atmospheric environment has been continuously improved. On this basis, it is also suggested to further improve residents' environmental awareness of using shared bikes, shared cars, subways and other public transportation tools to jointly improve traffic environmental pollution. At the same time, particulate pollution in indoor spaces cannot be ignored. The concentration and composition of indoor particulate matter are mainly determined by both outdoor infiltration and indoor source emissions (such as smoking, frying and barbecuing). The installation of fresh air conditioning system can effectively filter outdoor air pollutants. Quitting smoking and smoke-free cooking can significantly reduce indoor particulate matter production. We call on everyone to pay attention to air quality, enhance environmental awareness, and jointly safeguard our living environment.

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