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Review Article

Neurotoxicity related exposure to ambient nanoparticles

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Abstract

Air pollution exposure is among the most prevalent reasons for environmentally-induced oxidative stress and inflammation, both of which are implicated in the central nervous system (CNS) diseases. The CNS has emerged as an important target for adverse health effects of exposure to air pollutants, where it can cause neurological and neurodevelopmental disorders. Air pollution includes various components of gases, particulate matter (PM), ultrafine particulate (UFPs), metals, and organic compounds. An important source of PM and UFPM in the ambient air is associated with air pollution-related trafficking, and primarily diesel exhaust particles (DEPs). Controlled animal studies and epidemiological studies show that exposure to air pollution, and in particular urban air pollution or DEPs, may lead to neurotoxicity. In specific, exposure to air pollutants as an important factor may be in neurodevelopmental disorders (eg Autism) and neurological disorders (eg.., Alzheimer's Disease (AD)). The most noticeable effects of exposure to air pollutants in animals and humans are oxidative stress and neurodegeneration. Studies in rats exposed to DEPs showed microglial activity, increased lipid peroxidation, and neuronal accumulation in various areas of the brain, especially the olfactory bulb (OB) and the hippocampus (HI). Disorders of adult neurogenesis were also found. In most cases, the effects of DEP are more pronounced in male mice, probably due to lower antioxidant capacity due to less expression of paraoxonase 2.

More Information

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Introduction

Air pollution is a combination of various components, including gases, particulate matter (PM), metals, organic compounds, and the second factor is believed to be the most widespread health threat [1]. In many countries, especially South and East Asia, the population is often exposed to large amounts of PM (≥100 μg/m^3) [2]. PM is usually characterized by aerodynamic diameter: for example, PM10 is made up of particles with a diameter of 10 microns, while PM2.5 shows particles with diameters of less than 2.5 microns. It is also of paramount importance for PM (diameter UFPs < 100 nm) which can easily reach the general circulation and be distributed to various organs including the brain [3]. The UFPM can also through the nasal olfactory mucosa and reach first the olfactory bulb access the brain [4,5]. Diesel exhaust (DE) is the most important component in urban air pollution [6,7]. DE contains more than 40 toxic air pollutants, most notably fine particles (PM2.5) and ultra-fine particles [8,9]. Diesel engines provide power for a wide range of heavy equipment, vehicles, and other machinery used in countless industries including construction, transportation, agriculture, rail, marine, mining, and all kinds of factories. DE exposure is often used as a measure of traffic-related air pollution. Several million workers are sometimes or long-term DE exposure. Such occupational exposure to DEPs can also be very high [10]. The association between exposure to air pollutants, especially PM, and morbidity and mortality from cardiovascular and respiratory disease has been well established [11]. It is believed that such environmental toxicities are caused by oxidative stress and inflammatory processes [12]. Increased oxidative stress and inflammation following prenatal exposure to DEPs have also been demonstrated [13].

Neurotoxicity and air pollution exposure: experimental evidence and epidemiological

In recent years, evidence has been gathered from animal studies and humans epidemiological, suggesting that air

pollution may adversely affect the central nervous system and contribute to CNS disease [14-16]. PM2.5 and UFPM are of great concern because they can enter the bloodstream and spread to various organs, including the brain [3], In addition to direct access to the brain through the nasal olfactory mucosa [5,13,17]. Decreased cognitive function, olfactory dysfunction, hearing impairment, and auditory deficits, depressive symptoms, and other neuropsychiatric side effects in humans have been reported [18,19]. Also, acute exposure to DEPs has been shown to induce EEG changes [20]. Animal studies confirm human observations [1]. For example, dogs exposed to heavy air pollution provided evidence of neuroinflammation and neurodegeneration in different regions of the brain [12,14,21], And animals exposed to the air pollution in the highway tunnel had higher levels of inflammatory cytokines in different regions of the brain [22]. DE exposure causes altered motor activity, memory and learning, the ability to detect new objects and affective behavior, and to produce oxidative stress and neuronal accumulation in the CNS [23-25]. Besides, in our laboratory, we performed a series of studies in mice showing that chronic exposure to DEPs (350–400 μg / m^3 for 6 h) induces oxidative stress, activation microglia, neuro-inflammation and neurogenesis in different regions of the brain such as OB and HI [5].

DEPs exposure and neurotoxicity in mice

The DEPs consist of PM2.5 or smaller, with an aerodynamic mean diameter of 100 nm. In our previous studies, adult mice (age: 7-8 weeks) were exposed for 6 h/d to 350–400 μg/m^3 DEPs, and afterward investigated neurotoxic effects of DEPs exposure in adult mice [5]. At the end of exposure to DEPs, oxidative stress in brain areas was assessed by measuring lipid peroxidation, and some of the pro-inflammatory cytokines in (IL-1a, IL-1b, IL-6, TNF-α) was measured. Exposure to DEPs caused significantly increased lipid peroxidation and pro-inflammatory cytokines in the OB and the HI [5], while the antiapoptotic cytokine IL-9 decreased [26]. As described, mice exposed to DEPs had significantly higher levels of inflammatory cytokine and lipid peroxidation than control mice [5]. Various factors including sex, age, and genetic history can be modulated the susceptibility to airborne neurotoxicity [1, 27]. Gender differences are a variable that deserves further research [28] because the information is so limited. Gender differences in sensitivity to traffic-induced neurotoxicity may exist, and this may be due to differential expression of the antioxidant/anti-paraoxonase 2 (PON2) enzyme in the brains of males and females [29,30]. PON2 is an intracellular enzyme, capable of modifying reactive oxygen species and thus protecting cells against stress-induced oxidative toxicity, in addition to having anesthetic and non-inhibitory properties [30]. PON2 levels are inversely correlated with the degree of in vitro susceptibility to neurotoxicity causing oxidative stress. Studies show that in all brain regions and cell types surveyed, PON2 levels are higher in females than in males [31]. There are also gender differences concerning susceptibility to lipid peroxidation induced by DE and neurodegeneration *in vivo* [1,29]. Acute exposure to DEPs increased malondialdehyde (MDA) levels in the hippocampus 2.8-fold in males and only 1.9-fold in female mice. Also, the level of TNF-a in the hippocampus was increased 7-fold in males and 2.4-fold in females [32]. In all animals was observed a significant decrease in neurogenesis, which was more evident in female mice. Because air pollution may play a role in the etiology of neurodegenerative and neurodevelopmental diseases such as Parkinson's disease and autism, the prevalence of which is higher in males [33], such gender differences in sensitivity need to be further substantiated. Considering the general relationship of gene interactions with the environment in toxicology and risk assessment the likelihood that genetic polymorphisms may affect neurotoxic sensitivity due to air pollutant exposure should also be considered [34]. To test this hypothesis, one study used *Gclm* mice, which lack the modified subunit of glutamate-cysteine ligase, the first enzyme, and rate-limiting glutathione (GSH) synthase, a key player in cell defense against oxidative stress. Survey results showed that $Gclm^{-/-}$ mice have very low levels of GSH in all tissues including the brain [26], although they may regulate other antioxidant pathways. In contrast, $Gclm^{+/-}$ mice have only a modest decrease in GSH but may closely resemble a human Gclm polymorphism [35]. $Gclm^{-/-}$ mice are induced by neuroinflammation (levels of the pro-inflammatory cytokine IL-1b) and oxidative stress (lipid peroxidation) compared to wild-type ($Gclm^{+/+}$) mice induced by acute DEPs exposure [36]. Since several genetic polymorphisms of the enzymes are involved in oxidative stress and neural contamination, the possibility of genetic contamination based on neural contamination is warranted by future research.

Exposure to air pollution is a risk factor for neurological diseases

Animal studies and epidemiological surveys suggest that young people may be particularly vulnerable to the neurotoxicity of exposure to air pollution [37,38]. Studies in Mexico City have shown that In addition to the cognitive deficits, high levels of inflammation markers in the brains of children exposed to air pollution [39-41]. Hyperactivity in 7-year-old children is associated with early-life exposure to air pollution [42]. Exposure to air pollutants during pregnancy, in six European groups, was associated with delayed psychomotor development [37]. Some studies have shown that exposure to urban air pollution is inversely associated with sustained attention in adolescents [43], and to reduce cognitive development in preschool children [44]. Surveys' results show that DE exposure may cause neurotoxicity [45]. Maternal DEPs exposure (high levels,1.0 mg/m^3) causes changes in locomotor activity, impulsive behavior, and motor coordination in male mice offspring [46]. Behavioral alteration (enhanced bias toward immediate rewards), impulsivity-like behavior, and also long-term impairment of short-term memory, was reported following early postnatal exposure of concentrated ambient PM

in mice [47,48]. Depression-like responses in mice were caused following prenatal exposure to urban air nanoparticles [13,49]. Experimental surveys have shown that long-term exposure to DEPs in mice causes changes in motor activity, spatial memory and learning, and the ability to detect new objects, resulting in oxidative damage, neurodegeneration, and alterations in gene expression [23,50].

Autism is a type of neurodevelopmental disorder determined by a significant decrease in social and communication skills and the presence of stereotyped behaviors and the term autism spectrum disorders (ASD) is commonly utilized. Much attention has been paid to autism among the neurological disorders that may be associated with exposure to air pollutants, and some of the recent findings have found associations between exposure to urban air pollutants and autism [51]. The incidence of ASD appears to have increased over the past few decades, and is now estimated to be around 7-9/1000 [52,53]; ASD is also 4 to 12 times more common in males than females [33]. Symptoms of ASD usually present before the age of three and are often accompanied by abnormalities of attention, learning, cognitive function, and sensory processing [51]. Findings indicate that children with ASD have higher levels of oxidative stress [54,55], Also higher neuro-inflammation, microglia activation, and increased systemic inflammation [56,57].

Studies showed that residential proximity to freeways and prenatal and early-life exposure to urban air pollution was associated with autism [58,59]. Another epidemiological study had also similar results [60] and the other study showed that maternal exposure to DE was significantly associated with ASD, especially in boys [61]. Another study also showed an association between ASD and PM exposure, especially when exposure to PM occurred in the third trimester of pregnancy [62]. Also, a cohort study evidenced the higher susceptibility following exposure in the third trimester [63]. The results of some animal research are in agreement with human studies [1]. Reported that postnatal exposure to a high level of ambient air pollutants in male mice causes persistent various neurochemical changes, glial cell activation, and ventriculomegaly [64]. While has been shown that prenatal DEPs exposure, disrupt DNA methylation in the brain, especially affecting genes involved in neurogenesis and neuronal differentiation in mice [65]. Prenatal exposure to DEPs at urban air pollution relevant concentrations (350–400 $\mu g/m^3$) causes a behavioral alteration in adult male mice [13]. Human studies showed that when exposure occurs in the third trimester of pregnancy, the association between ASD and PM exposure is stronger [62,63], which in rats or mice, is equivalent to the first few postnatal weeks [66].

Many epidemiological studies that identify the effects of air pollutants exposure on behavior alteration, especially cognitive behavior, have shown significant effects also in the elderly. So, in addition to the susceptibility of the developing brain, the aging brain may also be especially sensitive to the neurotoxicity caused by exposure to air pollution [12,27,67,68]. As mentioned, the primary mechanisms of the harmful effects of air pollution exposure on the CNS appear to be related to neuro-inflammation and oxidative stress [14,69,70]. Air pollution is a CNS inflammatory prophylactic stimulus that has been largely overlooked as a risk factor for neurodegenerative diseases [71,72]. Diseases that are likely to be affected by air pollution exposure, including Parkinson's disease (PD) and Alzheimer's disease (AD), are also widespread [12,73]. PD is a devastating motor disorder and the second most common neurological disorder affecting 23-1% of the population over 50 years. Given these statistics, there is considerable concern that recent findings link air pollutant exposure to neurodegenerative and neuropathological conditions associated with PD and AD. In striking similarity, both AD and PD share primary pathology in OB, nuclei, and related pathways, with olfactory deficiency being one of the first findings in both diseases [12,74]. This work established the first link between exposure to pollution and accelerating the pathology of neurological disease. These findings have recently been confirmed and extended in humans and other animal models. Also, animal studies have shown that exposure to air pollution induces cytokine production [75,76], increased MAP kinase signaling [76], neurochemical changes [77], lipid peroxidation [75], and behavioral changes [27,78] Taken together, these studies show that air pollutants have CNS effects. Abnormal filamentous protein aggregates and neuritis are the common denominators of PD and AD [12,79]. While there are no studies yet to find a direct effect of air pollution on defined levy bodies (a pathological feature of PD) or beta-amyloid plaques (Ab) (a pathological feature of AD), exposure to urban air pollution causes neurological inflammation [12,39].

Therefore, humans and young animals may be particularly vulnerable to the inflammatory effects of exposure to air pollution, and these effects may accumulate throughout one's lifetime. Whereas ischemic stroke [80], multiple sclerosis (exposure to secondhand smoke increases risk) [81], and PD (airborne manganese content is associated with increased risk) [82]. Currently, only CNS diseases are epidemiologically based. However, given the high prevalence of PD and AD, the association between neurodegeneration and the pathogenesis of PD/AD, CNS pathology induced by air pollution, and the high prevalence of exposure to air pollution, the expansion of mechanical studies and Follow the epidemiological. The dangers of other CNS diseases are of concern to human health. As said, our studies in the behavioral alteration effects of exposure to DEPs in mice will be continues.

Conclusions and suggest further studies

Some recent studies suggest that the CNS may be an important target for exposure to air pollutants, and in particular nanoparticles in urban air, of which DEPs are a common source.

As mentioned earlier, there is a strong convergence between human epidemiological studies and experimental animal studies on the final biochemical and behavioral considerations that are affected by exposure to air pollution [1]. Exposure to air pollutants is problematic given the suggested link between air pollution exposure and neurological diseases such as ASD or dementia. Also, given that short-term exposure can cause biochemical changes associated with such diseases, exposure to air pollution in the workplace is usually low but can be very worrying. In general, further studies are needed to better describe the effects of air pollutant exposure on the CNS, its underlying mechanisms, and its role in the cause of neurological and neurodevelopmental diseases. In particular, due to the higher prevalence of developmental neurological disorders (such as ASD) and neurological disorders (such as PD) in men, gender may be affected by air pollution [28]. Given the complex nature of these common ambient toxins, CNS pathology is likely due to the synergistic interaction of multiple pathways and mechanisms, creating air pollutants in an environmentally relevant and important challenge. While epidemiology querying is associated with an increased risk of stroke, MS, and PD exposure to certain types of air pollution, further epidemiological and mechanical studies of the association between air pollution components and CNS disease are of particular importance to human health.

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