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Review Article

Exposure To Urban Air Pollution Nanoparticles and CNS Disease

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Abstract

Exposure to urban air pollutants has been established as a source of oxidative stress and neuroinflammation that causes central nervous system (CNS) disease. Nitrogen oxides, particulate matter (PM), including fine particles (PM with aerodynamic diameters ≤ 2.5μm, PM 2.5) and ultra-fine particles (UFPs, PM <0.1μm, PM 0.1), transition metals, and ozone are potent or oxidant capable of producing reactive oxygen species (ROS). While the mechanisms underlying CNS pathology due to air pollution are not well understood, recent findings suggest that changes in the blood brain barrier (BBB) and or leakage and transmission along the olfactory nerve into the olfactory bulb (OB) and microglial activation are the key factors of CNS damage following air pollution exposure. The incidence of stroke and the pathology of Parkinson's (PD) and Alzheimer's disease (AD) are associated with air pollution exposure. Some of the recent research shows that air pollutants reach the brain and in addition to cardiovascular and lung diseases, affect the health of the CNS too. This review cites evidence that exposure to air pollution fine particles is one of the causes of CNS disease.

Keywords: Air pollution exposure; Nanoparticles; Airborne particulate matter; CNS disease

Introduction

Recent studies report that the CNS may be a vital target for exposure to air pollutants, and especially for traffic air pollutants, of which diesel exhaust particles (DEPs) are common sources. As said earlier, there is a strong convergence between experimental animal studies and human epidemiological studies concerning the ultimate biochemical and behavioral considerations that are affected by air pollution exposure [1]. Furthermore, in vitro researches support the in vivo findings that exposure to DEPs activates microglia and stimulates neuroinflammation and oxidative stress [2-4]. The effects of air pollutants pass from periphery to the brain through systemic inflammation and the movement of UFPs into brain, where both physical properties of its particles and toxic compounds adsorbed on the PM can cause damage. Brain capillaries, astroglia, and especially microglia, respond to air pollution components by chronic activation, oxidative stress, and inflammation. Exposure to a high concentration of urban air pollutants is problematic given the proposed associations between exposure to air pollution and neurodegenerative diseases such as autism spectrum disorders (ASD) or dementia. Furthermore, given that even short-term exposure can cause biochemical changes associated with such diseases, air pollutants exposure in work places are commonly low but is also of very concern. Generally, other studies aimed at better describing the effects of traffic air pollutants exposure on the CNS, its role and its underlying mechanisms in the cause of neurodegenerative and neurodevelopmental diseases are indispensable. Especially, given the greater prevalence of neurodevelopmental (such as ASD) and neurological disorders neurodegenerative (such as PD) in males, gender may be affected by air pollution exposure [5].

Air Pollution Exposure and Developmental Neurotoxicity

Animal surveys and epidemiological surveys suggest that young people may be particularly vulnerable to the neurotoxicity of exposure to air pollution [6-11]. Hyperactivity in 7-year-olds is associated with air pollutants exposure early in life [12]. Research findings in Mexico City show that in addition to cognitive deficits due to exposure to air pollution, there is a high level of inflammatory markers in children's brains [6, 7, 13]. Prenatal

exposure to air pollution, in six groups, was related to delayed psychomotor development [11]. Some studies show that exposure to DEPs may cause neurotoxicity [14-16]. Research findings also show that exposure to urban air pollutants is inversely related to sustained attention in adolescents [17], and to reduce cognitive development in preschool children [18]. Prenatal exposure to the high concentration of DEPs (1.0 mg / m^3) causes changes in locomotor activity, impulsive behavior, and motor coordination in male mice [19, 20]. Behavioral alteration (enhanced bias toward immediate rewards), impulsivity-like behavior, and also long term impairment of short term memory, was reported following early postnatal ambient PM exposure in mice [16, 21, 22]. Exposure to UFPs in pregnancy causes depression-like responses in mice [23,24]. Experimental studies show that long term DEPs exposure 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 [25-28].

Autism is a type of neurodevelopmental disorder that characterized by a significant decrease in social and communication skills and presence of the stereotyped behaviors [29], and term of ASD is commonly utilized, include the autism and a range of the similar disorders. 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 research has found associations between exposure to urban air pollutants and autism. Symptoms of the ASD often present before age of three and usually accompanied by the abnormalities of attention, learning, cognitive function, and sensory processing [29]. ASD in the males is common 4 to 12 times more than females [30], and incidence of the ASD appears to be have increased over past few decades, that is now estimated to be around 7-9/1000 [31,32]. Findings indicate the higher levels of oxidative stress in the children with ASD [33, 34], also higher neuroinflammation, increased systemic inflammation, and microglia activation [35-38]. Studies showed that residential proximity to the freeways and prenatal and early-life urban air pollutants exposure was associated with autism [39,40]. Another study also showed a related between exposure to PM and ASD, especially when exposure to PM occurred in third trimester of pregnancy [41]. Another epidemiological study had also similar results [42] and the other study showed that maternal DE exposure was significantly related to ASD, especially in boys [43]. Also, a cohort study evidenced the higher susceptibility following exposure in the third trimester [44]. The results of some animal studies are consistent with human observations [1]. Reported that postnatal exposure to a high level of urban air pollution PM in male mice causes persistent various neurochemical changes, glial cell activation, and ventriculomegaly [45]. While has been shown that prenatal DEPs exposure, to disrupt DNA methylation in the brain, especially affecting genes involved in neurogenesis and neuronal differentiation in mice [46]. Prenatal exposure to DEPs at urban air pollution relevant concentrations (350–400 μg/m^3) causes a behavioral alteration in adult male mice [23]. Human studies showed that when exposure occurs in the third trimester of the pregnancy, association between ASD and PM exposure is stronger [41, 44], which is the equivalent to the first few of postnatal weeks in rats or mice [47]. As said, our studies in the behavioral alterations of exposure to DEPs encompassing both prenatal and the postnatal periods in the mice will be continues.

Air Pollution Exposure and Neurodegeneration

Many epidemiological studies that identify the effects of exposure to air pollutants on behavior, especially cognitive behavior, have shown significant effects also in the elderly. So, in addition to the susceptibility of developing the brain, also aging brain may be especially sensitive to the neurotoxicity caused by air pollution [48-51]. As mentioned, the primary mechanisms of the harmful effects of air pollutants exposure on the CNS appear to be related to neuroinflammation and oxidative stress [52-55]. There are amples evidence that neuroinflammatory and oxidative processes occur in the various neurodegenerative diseases [56, 57]. Air pollutants are the CNS inflammatory stimulants which have been largely overlooked as a risk factor for the neurogenic diseases. Furthermore, millions are exposed to the air pollutants in job disasters such as fires, war, and terrorist attacks [58]. Diseases that are likely to be affected by exposure to air pollutants, including PD and AD, are also widespread [59]. 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 the recent findings link exposure to air pollutants to neurodegenerative and neuropathological conditions associated with AD and PD. The earliest studies of this transplant were performed on populations of wild animals naturally exposed to contaminated urban environments [60].

The other of the important early symptom of the neurodegenerative diseases and particularly of PD is olfactory dysfunction [61], in which, actually precedes neuropathology in motor areas such as striatum and substantianigra, the OB is damaged [62]; in people exposed to high-level of air pollution, olfaction problems have also been reported [63]. Wild dogs living in areas of high contamination show enhanced oxidative damage, pre-puberty sporadic maturation, and the significant increase in DNA damage (apurinic /apyrimidinic sites) in OB, hippocampus (HI) and frontal cortex. Besides, dogs exposed to a high level of urban contamination exhibit accumulated metals (vanadium and nickel) and tissue damage in the target regions of the brain by gradient method (olfactory mucosa>OB > frontal cortex) and indicate Enter the nasal route as a key portal [60]. In striking similarity, both PD and AD share primary pathology in OB, nuclei, and related pathways, with olfactory deficiency being one of the first findings in both diseases [64]. This work established the first link between air pollution exposure and accelerating the pathology of neurological disease.

Recently, these findings have been extended and confirmed in animal models and humans. Brain tissue from highly infected

individuals showed increased CD-68, CD-163, and HLA-DR-positive cells (a marker of infiltrating monocytes or activation of resident microglia), increased pro-inflammatory markers, increased deposition of Ab42 (characteristic of AD protein), endothelial cell activation, BBB, [6] and brain lesions in frontal lobe [65]. The rearrangement of pro-inflammatory markers such as interleukin-1b (IL1-b) and cyclooxygenase 2 (COX2) as well as the CD-14 marker have been localized for innate immune cells in the frontal cortex, Niger essence, and vagal nerves [6]. In addition, animal studies have shown that exposure to air pollutants induces cytokine production [66, 67], increased MAP kinase signaling through JNK [67], lipid peroxidation, enhanced NFkb expression [66] neurochemical changes [68], and behavioral alteration [69] Taken together, these studies show that exposure to air pollutants has effects on CNS [70]. While there is no survey yet to find a direct effect of air pollutants on defined levy bodies (a pathological feature of PD) or beta-amyloid plaques (Ab) (a pathological feature of AD), urban air pollution exposure causes neurological inflammation [6]. For example, exposure to high dose of air pollutants in dogs, exhibits scattered amyloid plaque deposits a decade earlier than their fresh air exposure counterparts [60, 71].

In addition, accumulation of Ab42 and a-synuclein in early childhood begins [6] after high level of air pollutant exposure, from the view that exposure to air pollutants may cause premature aging in brain and/or stimulate disease progression. One of the plausible mechanisms is that nanoparticles [72-74] and oxidative stress [75-77] alter the accumulation and rate of protein fibrosis, potentially affecting the AB solution and a-synuclein. Changes in protein accumulation associated with exposure to air pollutants may be the primary pathology in neurodegenerative processes. Ambient toxins may exert their effects at various points throughout human development leading to CNS disease, a theory called the "multi-impact hypothesis" [78]. According to this assumption, studies show that PM affects the CNS at an early age [65]. For example, MRI analysis revealed structural damage (white matter lesions) in the frontal cortex in children exposed to high levels of air pollutants, potentially related to cognitive impairment [65]. Interestingly, air pollution exposure in the same condition in dogs also show vascular/endothelial pathology and neurogenesis of frontal lesions [65]. Therefore, the inflammatory effects of air pollution exposure may be harmful to humans and young animals, and these effects may accumulate throughout one's lifetime. Whereas ischemic stroke [79, 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. Many other unexplained diseases are likely to be air pollution exposed. These risks may be distributed between individual differences in population sensitivity, as genetic prediction may be vulnerable to CNS effects of air pollutant exposure, such as in inherited APOE4 allelic vectors [6] in humans *apo*E and knockout mice [83]. Due to the high prevalence of PD and AD, the association between neurodegeneration and the pathogenesis of PD/AD, CNS pathology induced by air pollutants and the high prevalence of air pollution exposure, the expansion of mechanical studies and epidemiological follow-up is needed.

Air Pollution Exposure and Ischemic Stroke

Human epidemiological studies and animal experimental surveys in recent years, suggesting that air pollutants may adversely affect to CNS and cause disease [84-86]. The impact of urban air pollutants on brain was first reported as an increase in the ischemic stroke in persons was internal coal smoke exposed. While it is clear that air pollution exposure can affect human health through respiratory, cardiovascular, and mortality complications, recently it has been shown also to have a detrimental effect on the brain [87, 88]. Whereas data on the association between ambient air pollution and cerebrovascular disease is limited, various air pollutants exposure (e.g., carbon monoxide, ozone, nitrogen dioxide, and particles) is epidemiologically at increased risk. It is associated with ischemic cerebrovascular events [79, 80, 89-91]. Indeed, current reports indicate that the risk of ischemic stroke is associated with exposure to air pollutants, even in relatively low pollutant communities [88, 89, 92]. Ozone and particles rapidly modulate the expression of genes involved in the major pathways of cerebrovascular vascularization, while pathological mechanisms are still unknown [91,93]. Current findings also show that effects of exposure to air pollutants invade brain parenchyma and cause pathological signs of neurological disease.

Conclusion

In conclusion, air pollutants are a mixture combination of ambient toxins that invade the CNS through several molecular and cellular pathways and cause disease. The effects of CNS are chronic, start in childhood, and may require time (years) to accumulate in the pathology. Particularly, exposure to air pollutants causes neuritis, oxidative stress, brain injury, and neuropathology. Either way, based on recent findings, the more emission from diesel engines than mentioned above has created a major concern that needs to be addressed with further studies into the health effects of UFPs exposure thus further experimental and epidemiological surveys of the association between UFPs and CNS disease are of particular importance.

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Contributions

All authors contributed to the study conception and design. The first draft of the manuscript was written by Mojtaba Ehsanifar and also he read and approved the final submitted manuscript.

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