JOURNAL OF BIOMEDICAL RESEARCH & ENVIRONMENTAL SCIENCES
issn: 2766-2276
SUBJECT AREA(S): BRAIN DISORDERS
DOI: 10.37871

REVIEW ARTICLE

Exposure to Air Pollution Nanoparticles: Oxidative Stress and Neuroinflammation

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ABSTRACT

Urban air pollutants exposure is known as a source of neuroinflammation and oxidative stress that causes the Central Nervous System (CNS) and neuropathology disease. Transition metals, Particulate Matter (PM), including PM 2.5 (PM <2.5 µm) and PM 0.1 (PM <0.1µm), nitrogen oxides and ozone are of potent or oxidant capable of producing Reactive Oxygen Species (ROS). Redox-sensitive pathways can be caused by oxidative stress, leading to various biological processes, including inflammation and cell death. The incidence of Alzheimer's Disease (AD) and Parkinson's Disease (PD) and stroke are associated with exposure to air pollution. Some recent findings suggest that urban air pollutants reach the brain in addition to pulmonary and cardiovascular diseases and affect the CNS health too. While the underlying CNS pathology mechanisms induced air pollutants exposure are not well understood, recent studies show that changes in Blood Brain Barrier (BBB) and microglial activation are key components. In this work, we reviewed the new evidence of the mechanisms by which ambient air pollution reach the brain and activate innate immune response as a source of oxidative stress and neuroinflammatory factors.

INTRODUCTION

While a variety of environmental factors are involved in neuronal inflammation leading to CNS disease, air pollutants may be the most common source of environmental oxidative stress and inflammation. In the chronic nature and pathology of CNS disease, inflammation is recognized as a risk factor [1]. Ambient air contains a complex combination of toxins, including gases, benzene, and Particulate Matter (PM) that can be irritating. Chemical composition of particles varies widely depending on geographic, meteorological, and specific source variables [2]. In general, ambient particles include elemental and organic carbon, inorganic components (trace metals, nitrates, sulfates, chloride, and ammonium), biological components (pollens, bacteria, and spores), volatile and semi-disintegrating organic compounds [3]. Furthermore, when the ambient particles are mixed with atmospheric gases (carbon monoxide, sulfur, ozone, and nitric oxides), they can form airborne particles. Environmental particles are commonly characterized by aerodynamic properties and their size and defined as PM2.5 and PM10 with diameters of less than 2.5 and 10 µm: PM with an aerodynamic diameter of 2.5 to 10 µm (PM10), PM smaller than 2.5 µm (PM2.5) and very small PM less than 0.1 µm or ultrafine PM (UFPs; <100 nm). This particles are acceptable fractions from different sources such as agricultural dust, wood combustion, road, vehicles emission, tire wear propagation, construction, mining operations, and demolition work [4,5]. PM2.5 due to heavy metals absorbed in pores and particle surfaces

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DOI: 10.37871/jbres1339

Submitted: 11 October 2021

Accepted: 19 October 2021

Published: 26 October 2021

Keywords

- Air pollution exposure
- Diesel exhausts nano-particles
- Airborne particulate matter
- Neuroinflammation
- Oxidative stress

MEDICINE GROUP

BRAIN DISORDERS

VOLUME: 2 ISSUE: 10 - OCTOBER

How to cite this article: Ehsanifar M, Banihashemian SS, Ehsanifar M. Exposure to Air Pollution Nanoparticles: Oxidative Stress and Neuroinflammation. J Biomed Res Environ Sci. 2021 Oct 26; 2(10): 964-976. doi: 10.37871/jbres1339, Article ID: JBRES1339, Available at: https://www.jelsciences.com/articles/jbres1339.pdf

produces more hydroxyl radicals, while larger particles (PM10) are mainly in the upper airways and it is purified by the mucosal system [6,7]. Diesel Exhaust Particles (DEPs), from vehicle emissions particularly diesel engines emission, are a main source of UFPs that may penetrate the home if poorly ventilated, where additional sources such as burning candles, cooking, chemical reactions, and tobacco smoke are also available [8]. However, attention has also been focused on nanoparticles less than 100 nm in diameter; UFPs are important because of their health effects such as chemical composition, high alveolar deposition fraction, large surface area, and ability to enter the bloodstream and cause inflammation [3,9]. The main route of air pollutant exposure is inhalation. The fine particles (PM2.5) are deposited in lungs, while the coarse particles (PM10) are filtered usually out by nose and the upper airways [3].

Recently, some findings support the involvement of neuroinflammation in pathogenesis of cognitive impairment and affective disorders [9,10]. For example, anxiety and depression in male mice and hippocampal inflammatory cytokine response and learning and memory disorder are related with DEPs exposure [10-12]. Traditionally, associated with an increased risk of cardiovascular and lung disease, now, air pollution exposure is also related to CNS diseases including stroke, Parkinson's, and Alzheimer's disease. Air pollutants are a multifaceted ambient poison that can attack the CNS through a variety of routes [3]. Now days, despite the varying chemical and physical properties of air pollution and their subsequent activation in multiple pathways, oxidative stress and inflammation are known to be the underlying mechanisms through which ambient air pollutants cause damage in the CNS [13]. In addition, while different types of cells in the brain are susceptible to air pollutants, new research suggests that capillaries and microglia may be important causes of cellular damage. This review corers the multifaceted mechanisms through which nanoparticles in the contaminated air affect the CNS as well as new mechanistic findings that contain chronic neuroinflammation and innate immunity in CNS disease caused by exposure to air pollutants.

Air pollution particles and health effects

Air pollution from traffic is a mixture that includes various components such as gases, Particle Matter (PM), organic compounds and metals [14]. Estimated that traffic pollution 20% to 70% of environmental pollution and 85% of ambient PM is related to traffic and resulting from vehicle combustion. So air pollution from traffic is one of the important sources of environmental pollution [7,15]. The association between exposure to urban air pollutant and mortality complications from respiratory and cardiovascular diseases is well established today, While new findings suggest that air pollutants exposure may also contribute to diseases of the CNS [12,16,17]. Some of the epidemiological surveys suggest that increased exposure to traffic air pollutant is associated with hearing and olfactory impairment, decreased cognitive function, as well as increased incidence of neurological pathology and depressive symptoms [18-20].

It is believed that exposure to PM is a very important threat between traffic air pollutant components and has been played a significant role in disease [17] (Figure 1). PM is broadly determined by size (aerodynamic diameter such as PM10 and PM2.5). UFPs is very worrying because these fine particles can easily enter bloodstream and after crossing the BBB, are transmitted to the brain and various organs [12,13]. Exhaust from diesel engines includes the complex mixture of hydrocarbons, gases, heavy metals, sulfur, particles and especially small sized PM produced in diesel fuel combustion [8,21]. Most DEPs are less than 1 micron in diameter and these particles are one of the main components of air pollutants [8]. DE is the main source of urban air pollution PM, which contains more than 40 toxic pollutants, especially UFPs. Some of the research to controlled Diesel Exhaust (DE) exposure has been investigated on human health. For example, following acute exposure to DEPs (300 µg/m3) in humans, it has been observed EEG changes [22]. DEPs contain many compounds that have potentially harmful effects on brain growth [23-25] and the immune system [26]. In 2013, DEPs was identified as a human carcinogen group 1 based on evidence of exposure to particles and lung cancer by the International Agency for Research on Cancer (IARC) [27,28].

As said, the mechanisms responsible for UFPs entry into brain are the main discussion topic, where active transport, BBB, and leakage and transmission along olfactory nerve into Olfactory Bulb (OB) have been proposed [12,29]. In spite of complex composition of urban air pollution, the classic surveys in cardiovascular system have shown that oxidative stress and inflammation are common mechanisms of air pollution injury [16,30,31]. Recent studies show that not only oxidative stress and inflammation are common concepts in neurodegenerative and CNS diseases, but current findings also point to a growing chain of evidence.

Exposure to air pollution: Oxidative stress and inflammation

In recent decades, due to the traffic of vehicles and other combustion processes, much attention has been given to exposure to air pollution. Gas and PM pollutants are very important factors in the urban areas, and various mechanisms have been proposed to explain the side effects of exposure to them on human health [32]. Although any air pollutant directly through the activation of intracellular oxidant pathways can exert its toxicity on cardiovascular and respiratory systems, particulates, ozone, and nitrogen oxides all have the same property of being strong oxidants, either through their direct effect on proteins and lipids

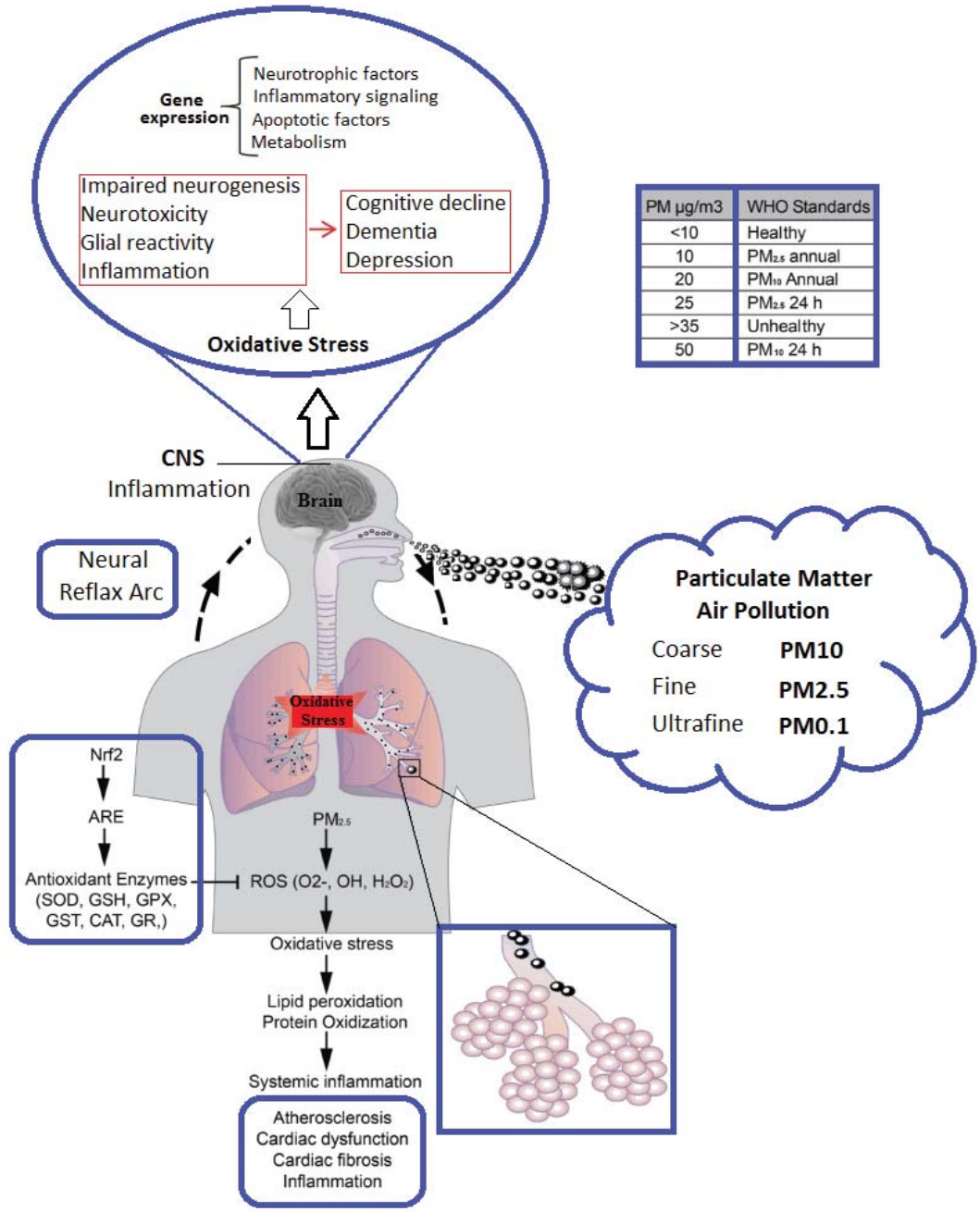

Figure 1 Air pollutants affect the brain in several ways. Air pollution Particulate Matter (PMs) is a complex toxin that causes a variety of pathologies in the CNS through several related mechanisms that may lead to CNS disease. Due to the complex nature of this environmental toxin, CNS pathology is probably due to the synergistic interactions of the multiple pathways listed here, and which causes air pollution nanoparticles to be a strong environmental exposure, in terms of Biological and be an important challenge for mechanical research. Depicts black dots of PMs.

[30,33-35]. Oxidative stress is in fact a biochemical imbalance that in which ROS production exceeds the capacity of the normal antioxidant. The biochemical imbalance can be caused by exposure to prooxidant air pollutants in the body. Uncontained ROS, in presence of oxidative stress, causes dysfunction and tissue damage by attacking and functional molecules (proteins, lipids, carbohydrates, RNA, DNA, NO, etc.) and denaturing structural, by modulating activities of redox-sensitive transcription factors [36,37].

ROS can generate by the particle surface where Polycyclic Aromatic Hydrocarbon (PAH) and nitro PAH are adsorbed, except for the transition metals (copper, iron, vanadium, and chromium) that catalyze the Fenton ($Fe^{2+} + H_2O_2 + H^+ \rightarrow Fe^{3+} + OH^{\cdot} + H_2O$) reaction [38,39]. Numerous researchers reported that some of the metals such as iron in the transition from the particles or through their presence on the particle surfaces are involved in production of ROS in the biological systems [37]. Besides, it should be

noted that nitrogen dioxide and ozone are oxidative DNA damage that they are usually associated with particles in ambient air [40,41]. Furthermore, photochemical oxidants (peroxyl acetate nitrate and ozone), secondary pollutants caused by sunlight in the atmosphere that contain reactive hydrocarbons and NOx, are involved in increasing oxidation stress. Then, if excess ROS is formed, mitochondrial damage occurs by induction of the NADPH Oxidase 4 (NOX4) isoform, together with activation of inflammatory cells (monocytes, neutrophils, and eosinophils) and an increase in the number of macrophages capable of ROS and reactivity nitrogen production [37,42-44]. At first, when oxidative stress is relatively low, for the formation of protection against undesirable biological consequences, various transcription factors, such as red blood cell Nuclear Factor (Nrf2), induce a series of antioxidant and detoxifying enzymes (catalase, glutathione S-transferase, and superoxide dismutase) that neutralize ROS [45-47]. Secondly, if the protective antioxidant response fails or is insufficient to counteract increased ROS production, it results in a pro-inflammatory state with various effects on cytotoxicity [48]. These effects are mediated by cascades of Mitogen-Activated Protein Kinase (MAPK) and NF-κB, which are responsible for expression of inflammatory biomarkers such as cytokines, chemokines, and adhesion molecules [47,48].

Essential pathways in response to toxic pollutants related to antioxidant enzymes and the proteins involved in phase II detoxification is first line of defense against oxidative stress. These responses are regulated by the Nuclear Factor-Erythroid 2-Related Factor 2 (Nrf2)/Antioxidant-Response Element (ARE) pathway. When oxidative and electrophilic chemical signals modify Kelch-like ECH associated protein 1 to release Nrf2, the pathway is activated, which then travels to nucleus and activates expression of antioxidant and phase II genes with ARE [36,47]. This pathway is important in mitigating oxidative stress-induced endothelial dysfunction [49]. Cytotoxic effects could occur at high concentration of pollutant exposure [47,50]. When these defense mechanisms are overwhelmed at a high dose of pollutants exposure induced oxidative stress, proinflammatory effects lead to via the activation of NFκB. The NFκB activation is increases transcription of chemokines, cytokines, and acute-phase proteins [51].

Findings show linkages of depressed antioxidant capacity and oxidative stress with the risk of hypertension [52], cardiovascular [30,53], and kidney disease [54]. Oxidative stress can play an important role in cardiovascular and respiratory effects of exposure to air pollution through the effects of the immune system and its ability to thrombogenic activity and initiate inflammatory process [16]. Experimental findings show that redox-active UFPs components following oxidative stress lead to ROS production in various cells in vascular tissues, blood, and the lungs. This can cause increased systemic inflammation, airway inflammation, and adverse cardiovascular reactions after overcoming antioxidants [50,55].

Epidemiological studies data that directly support this empirical evidence are limited, but there is indirect support for studies that have examined modification of responses to the exposure to air pollutants with a variety of genes associated with oxidative stress [56-61]. Also, some epidemiological studies reported that exposure to PM significantly increases the oxidative stress biomarkers in the blood, but surveys are limited for the populations exposed to air pollutants. Epidemiological data include panel investigation of healthy individuals with repeated criteria [62-65] and survey of workers exposed to smoke and aerosols of combustion [61,66-71]. Exposure to urban air pollution increases ox-LDL in mice [72] and impairs the anti-inflammatory capacity of the High-Density Lipoprotein (HDL) in the mice [73]. The secondhand tobacco smoke similar urban air pollution may have to carry redox-active components. It has been observed that low-density lipoprotein oxidation (ox-LDL) has increased among the people this smoke exposed [74]. Epidemiological studies show that the risk of atherosclerotic lesions is increased among the subjects living near heavy traffic [9,75-77]. Recent advances and findings have provided key insights into how exposure to air pollutants has harmful and dangerous effects on the brain. In particular, it is believed that air pollution exposure affects the brain in multiple pathways. Air pollutants are a mixture of toxin that causes a variety of CNS damage through multiple interconnected mechanisms that may cause CNS disease. While some of the air pollution effects have been attributed to the specific components of CNS, no specific pathway responsible for the CNS pathology has yet been identified. As said, given the complex nature of air pollutants, CNS pathology is most likely caused by the synergistic interactions of multiple pathways and causes air pollution to become an important challenge for mechanistic inquiry.

Oxidative stress responses, the importance of particle size and composition

In vitro results show that toxin compounds in PM such as transition metals and organic compounds (e.g., Cu, Fe, Zn, and Ni) are capable to produce ROS directly [50,61,78,79] or, as a result, their capacity to activate alveolar macrophages, respiratory endothelial and epithelial cells, and neutrophils or other leukocytes. Transmission metals through Fenton reactions have known the potential to stimulate oxidative stress. The ROS cellular generation has been demonstrated following exposed to PM mixtures using an invitro system of the rat alveolar macrophages [80,81]. Responsible for most of the PM emissions mobile-source are automobile exhaust [7,82], which produces nearly the complete set of pollutants [83]. One of the causes of oxidative stress is the important reactive chemicals, which may include PM2.5 organic components such as quin ones, which are PAHs or oxidized

PAH species that are converted to biotransformation using cytochrome P-450 1A1 to quinones [84,85]. DEPs are enriched in these redox cycling components [86]. Experimental findings show that PAH and themselves-oxidizing (e.g., quinones) in DEPs promote the generation of ROS, which leads to oxidative stress and inflammatory response resulting from NFkB activation [85,87,88]. Exposure to DEPs also leads to changes in the expression of antioxidant enzymes as shown in laboratory data [89] and studies of airway responses in humans [90] (Figure 2). These effects may underlie epidemiological findings of an increase in circulating inflammatory markers and excessive vascular hypercoagulability markers about exposure to ambient air pollutants in cross-sectional studies [91,92] and cohort panel studies [93-95].

The results of the chemical mass equilibrium model using the source tracer show that most PAHs come from vehicular sources. The biomarkers level of systemic inflammation were significantly associated with concentrations of both outdoor and indoor home of the low, medium, and high molecular weight PAHs [85,96,97]. Another study found that associations between plasma homocysteine levels with black carbon, and urban air pollutants [98,99]. Mechanisms have been suggested to explain these findings, including the inactivation of enzymes involved in homocysteinere methylation or involvement of pollutant-generated ROS. These results are consistent with the extensive literature review that has concluded that PM2.5 black carbon standard should be considered in line with national standards for ambient air quality standards in the United States, and "vehicular emissions are a main ambient factor in cardiovascular complications and mortality in united states" [61,100].

Also, the particle size has a vitally important determinant role of the chemical dose of redox-active, which is delivered to target organs. The UFPs (diameter <0.1 micrometers) and accumulation modes (PM2.5) make up the total mass of fine particles, which is regulated by United States Environmental Protection Agency (EPA). UFPs are expected to induce larger responses per unit mass than coarse particles that dominate PM2.5 mass. This is attributed to greater deposition and retention in lungs, the ability to escape phagocytosis by surface and large macrophages, and a higher number and surface area of fine particle, than larger particles, thus transferring and delivering more concentrations of toxic components to the lungs [50,61,101-104]. Due to this surface area, UFPs contain redox-active organic chemicals (such as PAH), and transport metals at concentrations much higher than coarse PM [105]. Even for low organic contents soot particles, the UFPs cell interactions may be an important the pro-oxidant mechanism that stimulates inflammatory responses, particularly in the lungs, possibly due to the carbon extensive reactive surface area [103,106]. Thus, the components of toxic particles and the effective surface area are not well-represented by EPA-regulated PM10 and PM2.5. However, some studies of cohort panels still showed

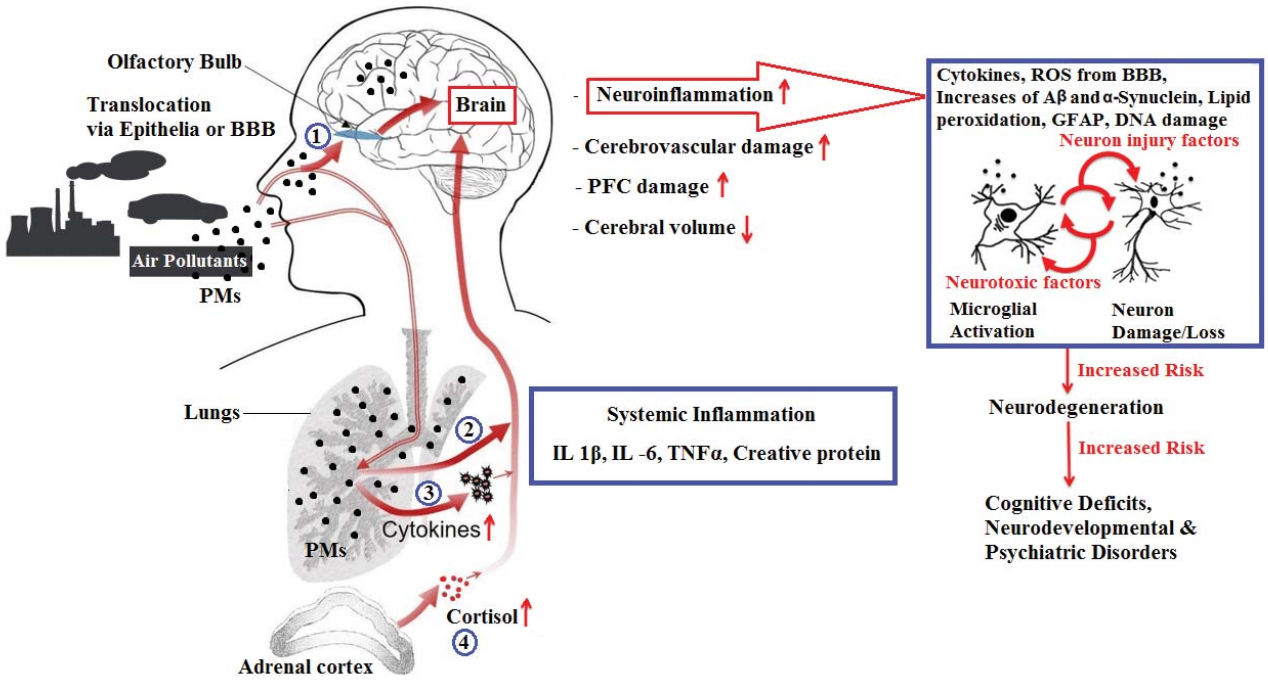

Figure 2 Air pollution nanoparticles can help activate toxic microglia by creating a reactive microglial cycle through three mechanisms: (1) Air pollutants components may directly activate microglia. (2) Cytokines from the peripheral systemic inflammatory response may activate microglia. (3) Particles, adsorbed compounds, or margin-derived cytokines may directly damage neurons and activate reactive micro gliosis. Thus, the components of air pollution cause reactive micro gliosis at several points in the cycle to lead to nerve damage. Depicts black dots of PMs.

associations of oxidative stress biomarkers with PM10 or PM2.5 mass [62,63,107,108].

Oxidative DNA damage (mainly 8-oxodG) in the lymphocytes following exposure to the high level of UFPs [64] and PM of metals [65] have been shown in two small panel cohort studies. However, the sample size was somewhat small due to the difficulty of performing 8-oxodG test on newly isolated lymphocytes. Besides, there is a few evidence of epidemiological study in humans that PM exposure is causing an increase in oxidative stress biomarkers in the blood. However, the movement of UFPs in the circulation have been demonstrated in several research, and despite its very low overall velocity, which is probably ≤1%, due to the high surface area and long shelf life, its effect on target organs may be significant [103,104] High retention of UFPs in the lungs, suggests that the effect of PM transfer through to the circulation is much greater [109]. This could be lead to lasting effects through the gradual transfer of redox-active component sin to circulation over a long time. And may be especially crucial for chemicals such as PAH that require biotransformation through phase I enzymes [110]. The results of a cohort panel study for UFPs showed that only pseudo-UFPs <0.25 micrometers (PM0.25) were significantly related with systemic inflammation biomarkers [TNFα and IL-6] [111] and are measured by ischemic ST-segment depression with outpatient electrocardiography [112].

PM itself contains ROS as well as active components of redox oxidation that can lead to the production of ROS by interaction with samples of biological origin. The capacity of inhaled PM to cause cell damage through oxidative reactions is called oxidative potential and can be measured using cell-free methods (Table 1).

Potential evaluation of PM components oxidation

Exposed to airborne particles, macrophages are first line of defense against lung damage. After phagocytizing the particles, following the cytokine cascades, the macrophages create ROS in an oxidative burst, leading to additional ROS production and inflammation. In this assay, the activity of cell-based ROS induced by aqueous particles extracts has been associate with organic compound concentration and the metal transition [2,80,113-115]. Also, in another study, the activity of ROS for PM0.25 was shown higher than that of larger particle fractions [115]. The association of the systemic inflammatory responses and the airway to the potential of collected PM to induce cellular ROS production was evaluated with both plasma NO and IL-6 measurements for 12 weeks in the sixty elderly subjects [116]. As described to evaluate the oxidative potential of PM, ROS production has been measured. Both IL-6 and NO exhalations were positively associated with macrophage ROS generation levels. The relationship of NO exhalation with ROS activity is not reflected by the mass concentration of PM0.25. But PM0.25 co-regression models with ROS production show that the oxidative potential of IL-6 has the highest association with PM0.25 mass [116]. In conclusion, the systemic biological indicators of inflammation are related to the ability of particles to induce ROS production by macrophages, and this relationship is nominally reflected by the mass concentration of the particles.

Cellular mechanisms of neuronal inflammation

Besides, recent studies, to understanding how air pollutants exposure affects the brain, surveyed the cell types that mediate the CNS pathology following air pollution exposure.

Astroglia

Astroglia plays an important role in BBB integration, maintains glia-neuron contact, maintains ionic homology, buffer excess neurotransmitters, and secrete nerve factors [117]. Storm activation occurs in response to a variety of CNS damage [118]. Accordingly, astroglia has been reported to be activated in humans that exposure to high doses of air pollutants, which is evident with increased Glial Fibrillary Acidic Protein (GFAP) [119,120]. Exposure to ozone in animal studies showed that local astrocytes near the brain capillaries increased the expression of TNFα and IL-6 [37,121]. Moreover, ozone exposure astrocytes in vitro result in the death of astrocytes [122]. Nevertheless, does astroglia respond to urban air pollutants, to oxidative stress and inflammation produced by other cell types or cell damage? It is unclear how astrology is activated in the brain.

Table 1: Biomarkers and methods of assessing oxidative stress.

Oxidative-stress assays		
ROS oxidative potential	**ERS, HRP/DCFH, DTT**	
Oxidative damage	**Proteins**	Oxidation level
	Lipids	Peroxidation level
	DNA	Deoxyguanosine modification
Detoxifying proteins	MAPK, Nrf2, PTEN, PI3K	
Antioxidant defense	GPx, SOD1, SOD2, XO, NOX	

Abbreviations: Cytp450: Cytochrome P450; CAT: Catalase; DNA: Deoxyribonucleic Acid; ERS: Electron Spin Resonance; DTT: Dithiothreitol; HPRT/DCFH: Horseradish Peroxidase/2070-Dichlorodihydrofluorescein; Gpx: Glutathione Peroxidase; NADPH: Nicotinamide Adenine Dinucleotide Phosphate; MAPK: Mitogen-Activated Protein Kinase; Nrf2: Nuclear Factor Erythroid 2-Related Factor 2; NOX: Nitric Oxidase; PTEN: Phosphatase and Tens in Homolog Protein; PI3K: Phosphoinositide 3- Kinase; XO: Xanthine Oxidase; SOD1: Superoxide Dismutase 1; SOD2: Superoxide Dismutase 2.

Microglia

Microglia are activated in response to pathogenic proteins in the body (eg. water and synuclein), cytokines, neurotoxicity, and environmental toxins (eg. paraquat and rotenone) [1,10], including air pollutants [123-125]. Microglia is of the brain innate immune cells that actively monitor the brain environment [126] and are activated in neurological diseases such as PD and AD [127,128]. Findings show that microglia mediate the neuronal damage because mixed cultures of neurons and moths treated with DEPs show selective dopaminergic neurotoxicity which occurred only in the presence of microglia [123]. It has been shown that microglia respond to the titanium nanoparticles by ROS production that is neurotoxic [129]. Also, it has been shown that microglia respond to PM in a laboratory study using DEPs. DEPs-treated cultures showed the microglial activation, as indicated by changes in the morphology and increased the production of superoxide, although PGE2, Nitric Oxide (NO), and TNFα were not detected [88,123]. Interestingly, exposure to concentrated air pollutants in vitro microglia, shows an increase in the mRNA expression for inflammatory cytokines, such as TNFα and IL-1b [10,12,124], suggesting that exposure to some forms of PM induces cytokine production. Besides, metal sin air pollutants activate microglia because microglia are *in vitro* activated by manganese [130], a component of industrial-induced air pollution. Further to neural death, disease proteins, and environmental stimuli such as air pollutants, microglia are also activated by the cytokines produced in response to the systemic inflammation, with catastrophic neurological consequences [131,132] and brain injury.

While most microglia activation is useful, activated microglia can be a chronic source of oxidative stress (•NO, H2O2, O•2—, ONOO•—/ONOOH) and inflammatory factors (TNFα, PGE2, and IFNg) in the brain [1]. Exposure to air pollutants can contribute to activation of the toxic microglial by activating the reactive microglia cycle through three mechanisms: (I) Air pollution components may directly activate microglia. (II) Microglia activated by cytokines arising from peripheral systemic inflammatory response. (III) PM, sorbents, or cytokines from margin may directly damage nerve cells to activate reactive microglia. Therefore, components of air pollutants may be interpreted as pathogens by microglia and lead to oxidative stress, chronic inflammation, brain vascular damage, and neurotoxicity.

Blood and brain barrier

Blood vessels throughout body show a wide range of different phenotypes that vary in function, gross structure, cellular structure, and blood exchange properties [133], which may be unique in their responses to air pollutants. Compared to most peripheral "leaky" vessels, brain microscopes (3 to 8 mm in diameter) are separated from many vessels because of a large barrier to macromolecules, small organic drugs, various toxins, and ions are. Therefore, these small vessels with in brain parenchyma from BBB [134]. The BBB is a physical and chemical barrier that protects different cell types, metabolic enzymes, and carrier proteins and protects brain from external insults. PM has been identified in both the human capillaries and brain parenchyma [120,135], indicating the ability to interact with both BBB-forming cells and to move within BBB through mechanisms still unknown. Recent findings have suggested that aluminum nanoparticles can increase oxidative stress, decrease the viability of human brain microvascular endothelial cells, alter mitochondrial potential, and reduce tight junction protein expression, suggesting that nanoparticles can endothelial cells damage and damage to BBB [136].

Exposure to air pollution is associated with increased ICAM and VCAM injury to brain endothelial cells [120]. Further, in vitro surveys using rat capillaries show that particle treatment induces the production of the cytokines and the ROS and that these signal caused changes in the expression and function of transmitters (eg: P-glycoprotein and resistance) [137]. Therefore, brain capillaries detect air pollutants and respond to these by regulating the function of the chemical and physical barrier and by producing inflammatory signals. Also, this response may act as an inflammatory sensor and finally contribute to the distribution of ROS, cytokines, and particles in the brain parenchyma, more likely in CNS pathology. Therefore, these findings are dependent on CNS drug therapy in neurodegenerative diseases. In particular, PM rearrangement induced by circulating transporters (multidrug resistance protein and p-glycoprotein in the BBB) in BBB may be have significant consequences for drug access to brain parenchyma for people living in heavily infected cities, be it [138-144].

Generally, human, animal, and cell culture research have shown that exposure to air pollutants causes CNS oxidative stress, nerve inflammation, nerve damage, BBB changes, abnormal filamentous protein reinforcement, and brain injury and pathways. This indicates through which air pollution is affected in the pathology of CNS disease. While empirical evidences are compelling, given nature of chronic air pollution exposure in humans, the effects of the CNS are likely to reflect exposure to pollutants throughout human life length, including critical growth and development periods. It is noteworthy that these chronic effects are not harmful by laboratory methods and short-term exposure to animals (Table 2). However, these important and empirical studies have provided the foundation needed to identify the air pollutants toxic components and opportunity to the address their role in the CNS disease and pave the way for rigorous empirical investigation at the epidemiological level.

Conclusion and Future Perspective

The air pollutants effects are transmitted from the periphery to the brain through systemic inflammation and the movement of UFPs to the brain, where both

Table 2: Effects of exposure to traffic air pollution particulate matter on brain.

Exposure Model of Air Pollution	Experimental Model	Pro-inflammatory Markers & Neuroinflammation	Behavior Changes& Neuropathology	References
Chronic Exposure to Urban Air Pollution	Human	IL1-*b*, COX_2, iNOS, & CD14 Increase	White Matter Lesions, Diffuse A*b*Plaques, BBB Damage, *a* Synuclein Aggregation, Cognitive Deficits, & DNA Damage	[119,120,136,140-142]
	Dog	NF*kb*, iNOS, & CD14 Increase	White Matter Lesions Diffuse A*b* Plaques *a* Synuclein Aggregation, DNA Damage, & BBB Damage	[141,143,144]
Exposure to Nanoparticles	Cell Culture	Microglial Activation	DA Neuron Damage	[145,146]
	Cell Culture Mouse	Superoxide Production N/T	Lower Tight Junction Expression Oxidative Stress (Brain)	[136]
	Mouse	N/T	Lipid Peroxidation, HBMEC Toxicity	[12,147-149]
	Mouse			
Exposure to Particulate Matter	Mouse	N/T	DA Neuron Damage in the	[150]
			Substantia Nigra	
	Mouse	TNF*a*, IL1-*b*, and INF*g*	Change in	[10,12,151]
		increase in OB	Neurotransmitters	
	Mouse	Cytokine Production, JNK	N/T	[152,153]
		Activation, Enhanced NF*kb*		
		Expression		
	Mouse	N/T	Changes in	[154]
			Neurotransmitters	
	Rat	N/T	Lipid Peroxidation,	[155]
			Decrease in Exploratory	
			Behavior	
	Cell Culture	Microglial Activation	DA Neuron Damage	[123]
		Superoxide Production		
	Cell Culture	Microglial Activation	N/T	[124]
		IL-6 & TNF*a*Production		
	Brain Capillary	TNF*a* & ROS	P-GP & MRP2 Increase	[137]
	Culture	Production	Tight Junction Protein	
		c-Jun Phosphorylation	Decrease	

Abbreviations: N/T: Not Tested; IL-1b: Interleukin 1b; DA: Dopamine; c-JNK: c-Jun N Terminal Kinase; INF*g*, Interferon *g*; TNF*a*: Tumor Necrosis Factor *a*; IL-6: Interleukin 6; NF*kb*: Nuclear Factor *kb*; P-GP: P-Glycoprotein; OB: Olfactory Bulb; ROS: Reactive Oxygen Species; BBB: Blood-Brain Barrier; MRP2: Multidrug Resistance Associated Protein-2; COX_2: Cyclooxygenase 2; HBMEC: Human Brain Microvascular Endothelial Cells.

the physical properties of the particles and the toxic compounds absorbed in the PM can cause damage. Cerebral capillaries, astroglia, and particularly microglia respond to the air pollutants components by oxidative stress, chronic activation, and inflammation. Exposure to urban air pollutants at high concentrations is problematic given the suggested association between air pollution exposure and neurodegenerative diseases such as AD or dementia. In addition, exposure to air pollutants in the workplace is usually low, but very worrying, given that even short-term exposure can cause the biochemical changes associated with such diseases. In general, other studies are needed to better describe the effects of exposure to traffic air pollutants on the CNS, its role, and its underlying mechanisms in the development of neurodegenerative and neurodevelopmental diseases. In particular, due to the higher prevalence of neurodevelopmental (such as AD) and neurological disorders (such as PD) in males, gender may be affected by exposure to air pollution [145-155]. In any case, according to recent findings, the higher emissions of diesel engines than the ones mentioned above have raised major concerns that should be addressed with further studies on the health effects of exposure to DEPs, so experimental studies and the epidemiological link between the DEPs and the CNS of the disease is of particular importance.

ACKNOWLEDGMENT

We thank Dr. Ehsanifar Lab. Tehran, Iran, for the support of this work.

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How to cite this article: Ehsanifar M, Banihashemian SS, Ehsanifar M. Exposure to Air Pollution Nanoparticles: Oxidative Stress and Neuroinflammation. J Biomed Res Environ Sci. 2021 Oct 26; 2(10): 964-976. doi: 10.37871/jbres1339, Article ID: JBRES1339, Available at: https://www.jelsciences.com/articles/jbres1339.pdf