Influence of Air pollution on Central Nervous System –An Overview

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Abstract:- Air pollution is a multifaceted environmental toxin capable of assaulting the CNS through diverse pathways. Air pollution is a complex mixture of environmental toxicants that assault the CNS through several cellular and molecular pathways to cause disease. Air pollution effects cross from the periphery to the brain through systemic inflammation, and translocation of nanoparticles to the brain, where both the physical characteristics of the particle itself and the toxic compounds adsorbed on the particle may cause damage. Air pollution has also been associated with diseases of the central nervous system (CNS), including stroke, Alzheimer's disease, Parkinson's disease, and neurodevelopmental disorders. Air pollution causes neuroinflammation, oxidative stress, microglial activation, cerebrovascular dysfunction, and alterations in the blood-brain barrier contribute to CNS pathology.

The central nervous system (CNS) is the target organ for the detrimental effects of airborne pollutants. Air pollutants such as gases (e.g., ground-level ozone, carbon monoxide, sulfur oxides, and nitrogen oxides), organic compounds (e.g., polycyclic aromatic hydrocarbons and bacterial endotoxins), and toxic metals (e.g., vanadium, lead, nickel, copper, and manganese) that can be found in outdoor and indoorair affect the CNS. Air pollution is a global problem and has become one of the major issues of public health as well as climate and environmental protection. Heavy traffic causes Air pollution, those effects on CNS damage and that there is a clear link between air pollution and neurological diseases. Understanding of the mediators and mechanisms of CNS injury due to air pollution will help to develop preventive and treatment strategies for the protection of individuals at risk.

Keywords: *Air pollution, Global problem, Central nervous system, Neuroinflammation.*

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I. Introduction

Air pollution has become a severe threat to our natural ecosystems and biodiversity in the environment. Both indoor and outdoor pollution of air adversely affects the health and well-being of all living beings. The sources of air pollution can either be natural (e.g., volcanic eruptions)or manmade (e.g. Industrial activities), and air pollution emerges as a serious health problem especially in rapidly growing countries. (Blockand Calder, 2009 andSermin*et al.*, 2011). Life expectancy has increased in last decades and health care improvements have contributed to people living longer. However, this has also contributed to increase the number of people with chronic disabling diseases such as Alzheimer (AD) and Parkinson(PD)(Miguel ,2015).The air pollution may affect the nervous system through a variety of cellular, molecular and inflammatory pathways that either directly damage brain structures or lead to a predisposition to neurological diseases. (Sermin*et al.*,2011). Air pollution represents a diverse mixture of substances including PM, gases (e.g., ground-level ozone, carbon monoxide, sulphur oxides, and nitrogen oxides), organic compounds (e.g., polycyclic aromatic hydrocarbons and bacterial endotoxins), and toxic metals (e.g., vanadium, lead, nickel, copper, and manganese) that can be found in outdoor and indoor air (Block and Calder, 2009, Craig *et.al.*,2008).

Thecentral nervous system (CNS) hasalsobeenproposedtobeatargetorganforthedetrimental effects of airborne pollutants (Oberd¨orsterandUtell,2002). The airborne pollutants can contribute to neurodegenerative disease processes already from early childhood on, especially if the individuals are chronically exposed to the contaminants (Block and Calder, 2009 and Calder´on-Garcidue˜nas*et al.*,2004 ; Calder´on-Garcidue˜nas*et al.*, 2008;Calder´on-Garcidue˜nas*et.al.*,2008). Air pollutants affect the CNS either directly by transport of Nano sized particles into the CNS or secondarily through systemic inflammations. Air pollution collectively describes the presence of a diverse and complex mixture of chemicals, particulate matter (PM), or of biological material in the ambient air which can cause harm or discomfort to humans or other living organisms.(Sermin*et.al.*,2012). Particulate matter (PM) air pollution is a leading public health concern across most of the populated world. (Wright and Ding, 2016).

Millions of people worldwide are chronically exposed to airborne pollutants in concentrations that are well

above legal safety standards (Block, 2009).The World Health Organization (WHO) estimates that air pollution is responsible for over 3 million premature deaths each year (Mills *et al*.,2009). Epidemiological and observational studies identified a strong link between the exposure to contaminants in the ambient air and adverse health outcomes, such ashospitalizationand mortality (Chen*et al*., 2008). .Exposuretoair pollutants has been associated with marked increases in cardiovascular disease morbidity and deaths resulting from myocardial ischemia, arrhythmia, heart failure, and respiratory diseases such as lung cancer and asthma (Mills *et.al*.,2009 and Chen *et al* .,2008).

Emerging evidence from recent epidemiological, observational, clinical, and experimental studies suggest that certain neurological diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), and stroke, may be strongly associated withambient air pollution. (Sermin*etal.*,2012).Diverse environmental factors have been implicated in neuroinflammation leading to CNS pathology, air pollution may rank as the most prevalent source of environmentally induced inflammation and oxidative stress (Craig *et al.,* 2008).Air pollution is now also associated with diverse CNS diseases, including Alzheimer's disease, Parkinson's Disease and stroke.(Michelle,2009).Inflammation and oxidative stress are identified as common and basic mechanisms through which air pollution causes damage (Mills *et al*.,2009) including CNS effects. Classic studies in the lung and cardiovascular system have revealed inflammation and oxidative stress as common mechanisms of air pollution-induced damage. (Riedl, 2008; Mills*et al.,* 2009;Muhlfeld*et al*., 2008;Simkhovich*et al.*,2008).Inflammation and oxidative stress are common denominators in neuropathology and CNS disease (Block et *al.,* 2007).

The impact of air pollution on central nervous system (CNS) outcomes including chronic brain inflammation, microglia activation, and white matter abnormalities leading to increased risk for autism spectrum disorders, lower IQ in children, neurodegenerative diseases (Parkinson's disease, PD; Alzheimer's disease, AD), multiple sclerosis, and stroke. (Michelle and Alison *et al.,* 2012).Nanoparticles are an important alternative in the development of treatment strategies for neurodegenerative diseases due to their small particle size, large surface and high drug loading efficiency, which allow them to cross the blood brain barrier and efficiently release specific drugs(Lietal.,2014; Leyva-Gómez *et al.*,2015). However, their small size allows them to penetrate the cell and organelles, disrupting their normal function (Buzea*etal.*, 2007).

II. Air Pollution Constituents

Air pollution represents a diverse mixture of substances including PM, gases (e.g., ground-level ozone, carbon monoxide, sulphur oxides, and nitrogen oxides), organic compounds (e.g., polycyclic aromatic hydrocarbons and bacterial endotoxins), and toxic metals (e.g., vanadium, lead, nickel, copper, and manganese) that can be found in outdoor and indoor air (BlockandCalder2009andCraig 2008). Roadandagriculturaldust, tire wearemissions, products of wood combustion, construction and demolition works, and mining operations are the primary sources of PM10. PM2.5 particlescommonlyoriginatefromoil refineries, metal processing facilities, tailpipe and brake emissions, residential fuel combustion, power plants, and wild fires (Craig, 2008).UFPs are mostly combustion-derived NPs, which can be produced by internal combustion engines, power plants, incinerators, and other sources of thermos degradation. They can carry soluble organic compounds, polycyclic aromatic hydrocarbons, and oxidized transition metals on their surface (Scheepers and Bos,1992).

Impact of air pollution on CNS

Air pollution is the introduction of harmful and unwanted substances like auto emissions, dust and gases, suspended particles, chemicals etc. into the air around us. Air pollutants might not enter the CNS directly, but could exert adverse eff ect on the CNS by triggering the release of soluble inflammatory mediators from primary entry organs or secondary deposition sites. Thereleaseofinflammatoryagentscouldthenlead to alter the susceptibility for neuroinflammation and neurodegeneration in the CNS. (Sermin*et al*., 2012). FinePMorNPscouldrapidly enter the circulatory system with the potential to directly aff ectthevascularsystem.Forinstance,NPscouldbeinhaled and cross the alveolar-capillary barrier in the lungs. The ability of NPs to cross this barrier is influenced by a number of factors that include the size of the particles, their charge, their chemical composition as well as their propensity to form aggregates. Even though the translocation of inhaled or instilled NPs(Nano-sized particles) across the alveolar-capillary barrier has been clearly demonstrated in animal studies for a range of NPs (Furuyama*et al.*,2009;Nemmar*et al.*,2002), it has been more difficult to directly demonstrate this mechanism in humans (Mills *et al.,* 2009). The very small UFPs(ultrafine) on the other hand easily penetrate cell membranes because of their large surface-to-volume ratio, which also enables them to traverse the classical barriers in the lung and the brain. Their ability to cross cell membraneseasilyexplainswhyPMcanbefoundinsideneurons or erythrocytes (Block and Calder, 2009;Valavanidis*et al.*, 2008). Another important and more direct route for UFPs(ultrafine) to enter the nervous system is through the

olfactory mucosa, which is a neuronal epithelium that is in direct contact with the environmental air (Lewis*et al.*,2005;Wang *et al.*, 2007; Wang *et al*., 2008). Additional direct neuronal entry routes for NPs (Nano-sized particles) have been described that involve the retrograde and anterograde transport in axons and dendrites such as the transport of inhaled NPs to the CNS via sensory nerve fibers that innervate the airway epithelia (Oberd¨orster*et al.*,2009). Ground-level ozone exposure activates the CNS through the vagal nerves without the involvement of the thoracic spinal nerves (Gacki`ere*etal.*, 2011). PM-related LPS (lipopolysaccharide) is likely to play an important role in these pathways, as shown by vagal upregulation of CD14 (Villarreal*et al.*, 2010). Many compounds within PM of various sizes are toxic to the developing and adult brain. (Wright and Ding, 2015). Long-term exposure to high PM concentrations can decrease total brain volume and increase the concentration of inflammatory markers (Wilker*et al.*, 2015).

Definition of air pollution

Air pollution is comprised of a diverse mixture of particulate matter (PM), gases (e.g. ground level ozone, carbon monoxide, sulphur oxides, nitrogen oxides), organic compounds (e.g. polycyclic aromatic hydrocarbons and endotoxins) and metals (e.g. vanadium, nickel, and manganese) present in outdoor and indoor air (Akimoto, 2003)

Effect of air pollution on human health

The accumulation outdoor air pollution may have a significant impact on central nervous system (CNS) health and disease. (Michelle and Alison *et al.*, 2012)

Stroke

Stroke or cerebral infarction is a sudden neurological deficit caused by an infarction (80% cases) or a hemorrhage (20% cases) in the brain. It is characterized by a quick onset (instantaneous or within minutes) and is most of the time affecting one half of the body: hemiplegia, unilateral blindness but also speech impairment. There are two types of strokes are there. They are Ischemic Stroke and hemorrhage.

Ischemic Stroke

The human brain is susceptible to grave harm from air pollution. Air pollutants can trigger strokes. They can also affect brain development and reduce human intelligence. Whenarmful air pollutants lead to inflammation and artery blockages in the arteries that nourish the brain, they can lead to stroke. Stroke is an important cause of incapacitation and of death.

Stroke is the second most prevalent cause of death and the leading cause of permanent disability globally. (W.H.O.2016). PM stimulates the pathology of ischemic stroke by initiating a systemic inflammatory response, generating oxidative damage, and contributing to the progression of cerebral atherosclerosisapproximately 80% of strokes are the ischemic type. They are caused by the occlusion of an artery delivering blood to the brain (brain arteries but also carotids and vertebral arteries). When this happens, a part of the brain is deprived of oxygen and nutrients. This deprivation results in a cerebral infarction, which provokes neurological damages that result in severe disabilities or death if it lasts more than several minutes or hours.

While it is well known that air pollution affects human health through cardiovascular and respiratory morbidity and mortality, it has only recently been shown that these deleterious effects extend to the brain. The impact of air pollution upon the brain was first noted as an increase in ischemic stroke frequency found in individuals exposed to indoor coal fumes(Zhang*et al.*, 1988; Michelle, 2009). While cardiorespiratory effects of air pollution have been extensively investigated (Mills, 2009).Only preliminary findings are available on the effects of airborne pollutants on the CNS. Stroke is one of the most prevalent CNS disorders which can be caused by air pollution (Mateenand Brook, 2011).Air pollution will continue to become a major health problem, especially in developing countries and rapidly growing economies (SerminGenc,2012). PM stimulates the pathology of ischemic stroke by initiating a systemic inflammatory response, generating oxidative damage, and contributing to the progression of cerebral atherosclerosis (Wright and Ding, 2016).The remaining 20% of strokes are hemorrhagic, subsequent to the rupture of a cerebral artery wall. Stroke can occur at all age, including childhood.

Alzheimer's disease

The brain disease that has come to be known as Alzheimer's disease was first described in November of 1901. The Alzheimer's symptoms that people hear about most frequently and are most familiar with are memory loss and getting lost. (JohnSchmid, 2008).

Alzheimer's disease (AD) is a loss of brain functions that worsens over time. It is a form of dementia. Alzheimer's disease damages the brain's intellectual functions. Short term memory often is affected early. Gradually other intellectual functions deteriorate. Judgment becomes impaired. Most people with advanced AD lose their ability to do normal daily activities Alzheimer's patients develop excessive deposits of two proteins in their

brains. Researchers believe that these proteins distort communication between brain cells. A chemical called acetylcholine may also be involved. It helps transmit messages between brain cells. Levels of acetylcholine begin to drop in patients with AD. This may add to the communication problems between brain cells. Eventually, brain cells themselves are affected. There is no way to prevent Alzheimer's disease. Regular physical exercise and a diet that includes fish, olive oil, and plenty of vegetables may delay the onset of symptoms and slow disease progression.

There is no cure for Alzheimer's disease. The goal of treatment is to manage symptoms and slow the progression of the disease. A class of drugs called cholinesterase inhibitors helps to restore communication between brain cells. These drugs may slow intellectual decline in some people with mild to moderate AD. They work by increasing the brain's levels of acetylcholine (https://www.drugs.com/health-guide/alzheimer-s-disease.html).Alzheimer's disease is the major form of dementia in elderly and possibly contributes to 60–70%ofcases.Itis a progressive, disabling and irreversible disease (GoedertandSpillantini, 2006). There are two recognized forms of AD. The first one is named familial or of early onset. The second one,thelate-onset or sporadic AD(Miguel,2015).Concomitant with a general increase in life expectancies worldwide, the incidence and prevalence of common neurodegenerative diseases grow as well, thereby increasing the financial and social burden on individuals and society. Alzheimer's disease (AD), the most prevalent neurodegenerative disease, is characterized by extracellular deposition of amyloid-beta (Aβ) peptide fibrils known as amyloid plaques and intracellular protein aggregates called neurofibrillary tangles (NFTs) (Ballard and Gauthieret.al, 2011). AD is the most common cause of dementia in aged people, aff ecting 27 million people globally.

Parkinson's disease

Parkinson's disease (PD), the second common neurodegenerative disorder, is caused by the degeneration of dopaminergic neurons in the substantia nigra and a progressive loss of dopaminergic neurotransmission in the caudate and putamen of the neostriatum(Shulman, and de Jager*et.al.*, 2011).Parkinson's disease is a condition in which parts of the brain become progressively damaged over many years. Parkinson's disease is caused by a loss of nerve cells in part of the brain called the substantia nigra. This leads to a reduction in a chemical called dopamine in the brain. Dopamine plays a vital role in regulating the movement of the body. A reduction in dopamine is responsible for many of the symptoms of Parkinson's disease. (http://www.nhs.uk/conditions/Parkinsons-disease/Pages/Introduction.aspx).

Parkinson's disease affects the way you move. It happens when there is a problem with certain nerve cells in the brain. Normally, these nerve cells make an important chemical called dopamine. Dopamine sends signals to the part of your brain that controls movement. It lets your muscles move smoothly and do what you want them to do. When you have Parkinson's, these nerve cells break down. Then you no longer have enough dopamine, and you have trouble moving the way you want to. Abnormal genes seem to lead to Parkinson's disease in some people. But so far, there is not enough proof to show that it is always inherited (https://www.webmd.com/parkinsons-disease/tc/parkinsons-disease-topic-overview#1).

Parkinson Disease is a chronic and progressive neurological disorder characterized by the selective loss of dopaminergic neurons of the substantia nigra pars compacta (SNpc). The cardinal features of the syndrome are related to motor dysfunction including tremor at rest, rigidity, akinesia (or bradykinesia), and postural instability. The motor symptoms appear when at least 60% of dopaminergic neurons are lost and 80–85% of dopamine content in the striatum is depleted (Jankovic, 2008; Wirdefeldt et al., 2011). PD is the second most common neurodegenerative disorder after AD. (Schrag et al., 2002; Jankovic, 2008).

The three main symptoms of Parkinson's disease are: involuntary shaking of particular parts of the body (tremor), slow movement, stiff and inflexible muscles. A person with Parkinson's disease can also experience a wide range of other physical and psychological symptoms, including: depression and anxiety ,balance problems – this may increase the chance of a fall ,loss of sense of smell (anosmis), problems sleeping (insomnia), memory problems. (http://www.nhs.uk/conditions/Parkinsons-disease/Pages/Introduction.aspx).In the later stages of the disease, a person with Parkinson's may have a fixed or blank expression, trouble speaking,andother problems. Some people also lose mental skills (dementia) (https://www.webmd.com/parkinsons-disease/tc/parkinsons-disease-topic-overview#1).

There is no cure for PD, and the existing therapies only provide brief relief of motor symptoms through improving the dopamine deficit or by surgical methods (Jankovic, 2008). Treatments are available to help reduce the main symptoms and maintain quality of life for as long as possible.These include:supportive treatments – such as physiotherapy and occupational therapy ,medication in some cases, brain surgery (http://www.nhs.uk/conditions/Parkinsons-

disease/Pages/Introduction.aspx).Parkinson's disease doesn't directly cause people to die, but the condition can place great strain on the body, and can make some people more vulnerable toseriousandlifethreateninginfections(http://www.nhs.uk/conditions/Parkinsonsdisease/Pages/Introduction.aspx).

Neurodevelopment and Mental Health

Normal brain development is a complicated process that involves controlled cell proliferation, neuronalmigrationfromtheirplaceofbirthtotheirfinallocation,andtheestablishment of specific connections between neurons and target tissues (Grandjean and Landrigan, 2006). All of these processes are tightly controlled, but are also influenced by environmental conditions. Air pollutants can affect the brain at any age, but the developing brain is particularly vulnerable because of its high neuronal proliferation and differentiation rates and its immature metabolism and imperfect BBB (Sunyer, 2008). Disturbances of developmental processes in the brain can lead to permanent abnormalities that translate into later life.

Neuroinflammation and Inflammasome Activation

Neuroinflammation is a complex and innate response of neural tissue against harmful stimuli such as pathogens, damaged cells, and other irritants within the CNS. A crucial component of innate immunity in the CNs involves the production of proinflammatory cytokines mediated by inflammasomesignalling (Chakraborty, 2010). PM initiates a cascade in the lungs that leads to the build-up of reactive oxygen species (ROS) and the development of systemic inflammation (Wright and Ding, 2016).

Microglial Activation.

Microglia are the resident innate immune cells in the brain and are predominant regulators of neuroinflammation, evidenced by their production of pro-inflammatory (e.g., Interleukin-1!tumor necrosis factor (TNF)-α, prostaglandin E , and interferon-γ) and reactive oxygen species (e.g., NO, H O , O , and ONOO /ONOOH) (Block et al. , 2007).

Microglia, the macrophage-like cells of CNS, are the principal players in the brain's innate immune response. They are the immunocompetent cells of the brain that continuously survey their environment with highly motile extensions (Ransohoff and Cardona,2010) Microglia cells rapidly change their cell morphology in response to any disturbance of nervous system homeostasis and are then referred to as activated on the basis of morphological changes and expressionofcellsurfaceantigens(Ransohoff and Cardona,2010). The microglia are necessary for normal brain function, excessive and chronic activation can result in neurotoxicity, such as the initiation and/or amplification of neuronal damage (Block and Hong, 2005).The microglia are activated in neurodegenerative diseases, as indicated by analysis of post-mortem brains from AD and PD patients (McGeer*et al*.. 1988), and have been implicated in the progressive nature of each disease (Block and Hong, 2005, 2007, Lull and Block, 2010, McGeer and McGeer, 2010). Microglia are also activated in the pre-frontal cortex of autistic children (Morgan *et al.*, 2010) and in response to ischemic stroke (Yenari*et al.*, 2010) (Michelle and Alison *et al.*, 2012). The air pollution may be a common and continuous environmental source of microglial activation. (Michelle and Alison *et al.*, 2012).

Oxidative Stress

Oxidative stress refers to an imbalance between the productions of ROS (Reactive oxygen species)andthecellsabilitytodetoxifyreactiveintermediatesor to repair cellular damage caused by ROS. They are highly reactive molecules because of their unpaired electrons and form as natural by products of a cell normal oxygen metabolism. They also full important roles in cell signalling and homeostasis (SerminGenc, 2012).

Alterations in the Blood-Brain Barrier

TheBBBisthemajor site of controlled blood-CNS exchange. This physical barrier protects the CNS from potential toxins and pathogenic agents. An intact BBB is important for the proper functioning of the CNS by actively controlling cellular and molecular trafficking between the systemic circulation and the brain parenchyma. (Abbott and Patabendige, 2010).The BBB integrity is impaired in many common CNS disorders such as AD, PD, and stroke. (Palmer, 2010). Therapeutic strategies that aim to change BBB permeability may combat neurotoxic effects of air pollutant on the CNS.

III. Conclusion

Air pollution isaglobal problem and has become one of the major issues of public health as well as climate and environmental protection. The traffic-derived pollution, causes CNS damage and that there is a clear link between air pollution and neurological diseases. Airborne particles cause neuropathology, which seem to be mediated by direct or indirect proinflammatory and oxidative responses. The understanding of the mediators and mechanisms of CNS injury due to air pollution will help to develop preventive and treatment strategies for the protection of individuals at risk. Improving air quality standards, minimizing personal exposures, and the redesign of engine and fuel technologies will also reduce air pollution and its consequences for neurological morbidity and mortality. Decreasing PM

concentrations in urban centres around the world would increase the quality of life and life expectancy, in part, by protecting the CNS from inflammatory stressors and atherosclerosis.

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