Nitrooxidative Stress and Neuroinflammation Caused by Air Pollutants

Subjects: Neurosciences

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Millions of people around the world are exposed to air pollutants, such as particulate matter 2.5 ($PM_{2.5}$) and ozone (O_3). Such exposure usually does not exclude these two types of pollutants and their harmful effects could be additive or synergistic. O_3 is a highly oxidizing gas that reacts with the cellular environment just as $PM_{2.5}$, triggering nitrooxidative damage.

particulate matter air pollution oxidative stress

1. Introduction

Human health depends greatly on the functionality of homeostatic protective mechanisms, which is at the first relay on maintaining the REDOX balance. This is related to the equilibrium between the presence, formation, function, and neutralization of reactive oxygen and nitrogen species (RONS), which in excess cause nitrooxidative stress, as well as their metabolites. These reactive species are counteracted by the activity of the endogenous antioxidant defense system (EADS), like catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), and heme oxygenase-1 (HO-1) [1][2][3]. One of the sources responsible for the excessive RONS formation is exposure to environmental pollutants. Endogenously, the metabolic activity leads to the formation of RONS, and, usually, their rate of formation is neutralized by EADS [1], but a persistently high concentration of pollutants triggers RONS formation far beyond the neutralizing capacity of EADS. Recognized pollutants include pesticides, herbicides, drugs, heavy metals, toxic gases, particulate matter 10 (PM_{10}), 2.5 ($PM_{2.5}$), and ultrafine particulate matter (UFPM). Most of these pollutants share an anthropogenic origin and other organic pollutants like bacterial lipopolysaccharide (LPS) are frequently present [4][5][6][7][8]. Common air pollutants are nitrogen oxides (NOx), sulfur dioxides (SO_2), and ammonia (NH_3), among others, which are emitted in the gas phase; then, they undergo a photoreaction process (sun UV radiation) and, consequently, secondary pollutants like ozone (O_3) are formed and their gaseous nature is preserved [9].

The air quality guideline levels (AQGL) established by the World Health Organization (WHO) in 2005 for $PM_{2.5}$ in a 24 h exposure is 25 $\mu g/m^3$ with an annual average of 10 $\mu g/m^3$ as permissible, and for PM_{10}, the daily exposure is 50 $\mu g/m^3$ with annual average of 20 $\mu g/m^3$. In 2021, these guidelines changed to 5 $\mu g/m^3$ for $PM_{2.5}$ in 24 h exposure with an annual average of 15 $\mu g/m^3$, and 45 $\mu g/m^3$ for PM_{10} in a daily exposure with an annual average of 15 $\mu g/m^3$. Improving AQGL is a global challenge that has not been accomplished. With respect to O_3, the AQGL in 2005 was 100 $\mu g/m^3$ (50 ppb = 0.050 ppm) in a 24 h exposure and they remained unchanged in 2021 [10].

Particularly, the interest is focused on the harmful effects exerted by two air pollutants: $PM_{2.5}$ and O_3 in the central nervous system (CNS). These pollutants can induce RONS formation after their entry into the respiratory system and spread throughout the body, damaging the brain–blood barrier (BBB) and, finally, altering the brain homeostasis; all these events occur in an indirect route. These pollutants may also simultaneously reach the CNS through a direct route that initiates in the olfactory mucosa and reaches important brain structures like the olfactory bulb, entorhinal cortex, hippocampus, brain cortex, cerebellum, and brain stem [11][12][13][14].

2. Origen and Nature of PM

PM is classified depending on the particle size and the diverse substances contained in each PM. The main PM sources are oil refineries, factories, incinerators, forest fires, internal combustion motors, cement factories, and the construction industry, among others. Oil PM_{10} is mainly composed of particles ranging from 10 µm to 100 µm; however, the peak abundance is located between 20 to 30 µm. Despite this estimation, there are differences in their distribution among different geographical locations. Particles above 100 µm are not considered because of their faster sedimentations on the ground surface due to the Earth's gravitational force [15]. These PM_{10} are composed of fossil fuel combustion (black carbon or soot), volatile organic compounds (VOCs: benzene, aldehydes, carbon monoxide, ethylbenzene, and 1,3-butadiene, and others), mineral dust or ash (Mg, Al, Ca, Cr, Fe, Ni, Cu, Zn, and Pb, among others), sea or lagoon spray (H_2O, ammonia, H_2O_2), inorganic aerosols (secondary), toxic gases, and organic matter (LPS) [16][17]. In highly populated cities, the most common source of fossil fuel combustion is the exhaust emission of internal combustion vehicles; thus, for a larger car density, a higher load of PM_{10} will be generated. The black carbon core (BCC) is less oxidized than the peripheral sheet by the effect of combustion. These particles do not penetrate the lungs, so their toxic effects are limited to the upper respiratory tract [17].

The composition of $PM_{2.5}$ includes the (BCC), with adsorbed volatile organic compounds, material of organic nature, ions (sulfate, nitrate, ammonium), gases (NO_2, CO, SO_2) heavy metals, toxic gases, oxidized carbon, biological molecules, and VOCs, among others, which are particularly located in the corona zone of PM. $PM_{2.5}$ possesses an aerodynamic size that enables their access to the pulmonary alveolar epithelium and causes local and systemic damage. These substances exhibit site- and time-dependent variations [17][18]. The black carbon particle may have a very diverse load of substances depending on local relative abundance; for instance, a heavier load with LPS may be expected in places where sanitary facilities are scarce and animal and human feces are on the ground surface. In other places, the proximity of factories with chimneys will contribute to the load of toxic gases, ammonia, or other harmful substances.

The UFPM (<0.1 µm) exhibit a smaller diameter than $PM_{2.5}$ and they also easily reach the alveolar epithelium and may cause damage [19]. In spite of its small mass, UFPM may account for higher particle counts than $PM_{2.5}$ and PM_{10}. Thus, in terms of health hazards, UFPM can be considered among the most reactive because their surface allows great adsorption. UFPM easily reaches the alveolar epithelium and penetrates this barrier reaching blood circulation, throughout which they can systemically spread to all tissues and organs. UFPM may contain important amounts of toxic gases like NOx, O_3, SO_2, NH_2, trace metals, and organic matter (e.g., LPS) [19].

3. Nitrooxidative Stress by $PM_{2.5}$ in the CNS

Controlled exposure to $PM_{2.5}$ in experimental models is necessary to identify and characterize the initial changes that lead to systemic injury or complications and brain damage. In this context, the effect of $PM_{2.5}$ has been approached in a model of single- and three-time repeated exposure model by intranasal instillation. Interestingly, NO was the initial oxidant molecule generated as inducible nitric oxide synthase, which was overexpressed in lung lavages 30 min after a single exposure, causing vascular endothelial dysfunction [20]. This event was followed by a second round of oxidative stress evidenced by the formation of malondialdehyde (MDA) as an indicator of lipoperoxidation caused by other oxidant species like H_2O_2. Thus, $PM_{2.5}$ exposure induces nitrosative stress (NS) caused by nitrogen reactive species (RNS), earlier than the oxidative stress (OS) caused by oxygen reactive species; they both continue the production of nitrooxidative stress (NOS) caused by reactive nitrogen and oxygen species. These observations suggest that $PM_{2.5}$ induces nitrooxidative stress in a sequenced manner [20]. Thereafter, Piao et al. [21] reported that exposures to $PM_{2.5}$ by intranasal instillation induced oxidative stress and inflammation in a mouse model of allergic rhinitis through the activation of the Nrf2/NFκB signaling pathway. However, a major concern arises considering $PM_{2.5}$ caused spatial learning and memory impairment, affecting inquiring ability, and sensory function. These alterations were supported by ultrastructural analysis where mitochondrial changes, myelin sheet disarrangement, and neuronal apoptosis occurred [21][22]. The exposure of rats to an experimental load of ambient dusty PM from 200 to 500, 500 to 2000, and 2000 to 8000 $\mu g/m^3$ caused BBB damage, OS, increased concentration of inflammatory cytokines, and brain edema. These changes were associated with impaired spatial memory and hippocampal long-term potentiation (LTP) [23]. It has been proposed that $PM_{2.5}$ is capable of inducing changes in platelet parameters, megakaryocyte activation, OS, and neuroinflammation that lead to the development of ischemic stroke, thus becoming an additional risk factor aside from those previously described [24]. $PM_{2.5}$ exposure has also been associated with an increase in cases of children affected by autism spectrum disorder [25].

4. Transcriptional Factors Activated by PM

The exposure to $PM_{2.5}$ induces the formation of RONS which are responsible for a milliard of consequences that alter homeostasis. Some of these consequences include the activation of transcriptional factors like Keap1-Nrf2-ARE, NFκB, TLR, and MAPKs, which modify the expression of genes involved in important mechanisms to recover homeostasis through adaptive changes [26].

The axis Keap1-Nrf2-ARE is an important signaling pathway that, when activated, induces the expression of antioxidant and cytoprotective gene responses. The oxidation of serine residues in Keap1 by RONS allows the release of Nrf2 from Keap1 and Cul3, which are degraded by the proteasome. Once Nrf2 is released, it undergoes nuclear translocation, forming a heterodimer with Maf and binds to the antioxidant response elements (ARE), and thus the expression of antioxidant enzymes and cytoprotective proteins increases. If Nrf2 is not released Cul3-Keap1 regulates Nrf2 polyubiquitination leading to its proteasomal degradation [27]. The antioxidant response mediated by Nrf2 activation includes the expression molecules that are part of the AEDS like CAT, SOD, and GR.

However, this can be overcome if the exposure to exogenous oxidant agents, like PM or O_3, is intense and prolonged [28].

The other transcriptional factor that plays an important role in the inflammatory response is NFκB. In healthy cells, this factor is localized in the cytosol as a heterotrimeric complex formed by the subunits p65/p50 with its bound inhibitor subunit (IκB), which avoids NFκB nuclear translocation. However, when an adequate signal occurs (e.g., oxidative damage), IκB is rapidly ubiquitinated and degraded in the proteasome; once released, the p65/p50 dimer undergoes nuclear translocation and binds to its response elements, inducing the expression of diverse molecules including inflammatory cytokines and pro-oxidative enzymes among others [29]. A remarkable protein induced by NFκB activation is KEAP1, which plays an important role in regulating the activation of the transcriptional factor Nrf2 [30]. During the exposure to PM, NFκB becomes activated by OS, which induces the activation of its kinases, IKKα and IKKβ, while IKKγ (NEMO) acts as a regulatory subunit [31]. These kinases are also activated by the TNF receptor, Toll-like receptor, and interleukin receptors in the canonical pathway, while the non-canonical activation requires the stimulation of specific TNF receptors that lead to the recruitment of TRAF2 and TRAF3 [32]. This pathway continues with the activation of NFκB-inducing kinase. RONS are also capable of activating NFκB through alternative phosphorylation of IκBα (NFκB inhibitor). The phosphorylation by RONS is mediated by casein kinase II, particularly in tyrosine residue 42 and other tyrosine residues in IκBα [32]. Furthermore, RONS like H_2O_2 can activate IKKs through the formation of disulfide bonds between cysteine residues 54 and 347. Thus, the release of NFκB dimers (p50/p65) translocates to the nucleus and binds DNA, increasing the expression of inflammatory cytokines (TNFα) and interleukins (IL-1β, IL-6, IL-11, IL-17), as well as pro-oxidant enzymes (iNOS, COX-2, LOX-5, LOX-12) [32]. NFκB activation by RONS induces the expression of inflammatory cytokines, which, after binding to their receptors, may overactivate NFκB, leading to an amplified pro-oxidant and inflammatory response.

An important feature of the crosstalk between Nrf2 and NFκB is that, upon activation of NFκB, the expression of Keap1 is increased, leading to its binding to Nrf2 and its consequent proteasomal degradation and the decreased expression of antioxidant enzymes [30].

5. Human Brain Damage by PM

Studies on the effects of highly polluted air in megacities have been reported by Calderón-Garcidueñas since 1992 [33], where total pollutant load was associated with a variety of alterations in diverse human and dog tissues and organs [34]. However, it was not until 2015 that $PM_{2.5}$ was associated with specific disease markers for obesity, Alzheimer's disease (AD), non-Alzheimer's dementia (N-AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and others [4][35][36]. Furthermore, PM_{10}, SO_2, NO_2, and NO have been associated with worsening multiple sclerosis (MS) outcomes, hypothesizing that oxidative stress and inflammation damage BBB lead to chronic neuroinflammation. These events could be followed by an immune attack reinforced by transcriptional factors involving activated microglia (microgliosis) that attack neuronal tissue and contribute to an important decrease in self-tolerance and possible production of autoantibodies [37][38]. PM air pollution has also been associated with pre and postnatal CNS damage, particularly the increasing incidence of autism and autism spectrum disorder (ASD) that has been reported [25][39][40].

Prenatal exposure to PM in highly polluted urban zones has been associated with developmental retardation of brain maturation processes [41]. Such retardation may contribute to the onset of neurological conditions like schizophrenia and ASD that are clinically diagnosed in early childhood. Furthermore, the alteration in brain development is evidenced by decreased intellectual performance, behavioral alterations, cognitive disorders, memory consolidation, and motor language difficulty [42][43], and boys are apparently more susceptible than girls.

When exposure to $PM_{2.5}$ increases between 5 months before birth and 1 month after birth (perinatal), additional changes occur and neurodegenerative disease markers are detected [44][45].

The maturation of the human brain in boys apparently requires an extended period; thus, the EADS is not quite efficient, and exposure to $PM_{2.5}$ and NO_2 causes profound damage, as previously documented. The detrimental effects were significant in memory and verbal performance. Furthermore, affectation in global cognition, including numeric and motor skills were affected mainly by NO_2 [43]. The most important effects could be due to oxidative stress, systemic and neuro-inflammation, as well as decreased fetal growth. These differential adverse effects may be due to a wider sensitive window for boys and narrower for girls; could it be attributable to a faster maturity process of the EADS for the female brain? In experimental models, similar observations have been documented with the additional control of sex and exposure period (pre and/or postnatal). Learning, memory, and behavioral flexibility were affected leading to an impulsivity-like behavior. There were differences in the amino acid pool probably related to sexually differentiated neurotoxicity, in spite of microglia being persistently activated in both males and females [19][46].

Exposure to $PM_{2.5}$ in early postnatal life leads to an increased risk of developing attention deficit hyperactivity disorder (ADHD) and ASD. As exposure to $PM_{2.5}$ in early postnatal life occurs in a continuous manner, the alterations in neuronal development are difficult to discriminate from other potential factors [47]. Furthermore, the standardization of experimental models faces serious difficulties due to the neurodevelopmental velocity in animal models (28 days) versus the three years required in human beings. Thus, even the sequence of damage to involved molecules and the response capacity of the organisms may be different in both cases.

The effects of air polluted with PM in late childhood (3 years and over) have been associated with the onset of anxiety and depression symptoms, and ADHD also increases. Thus, it would be important to develop strategies to mitigate the impact of air pollution on children's health. As exposure of children becomes harder to control, the risk of exhibiting improper behavior and emotional distress increases. When exposure time increases in childhood, the incidence of criminality may also increase for teenagers. These and other issues regarding the consequences of uncontrolled inhaling of PM using experimental models or data obtained and analyzed from human populations require further study [47][48].

As people arrive at adult age, the exposure level to air pollution increases due to economically remunerated work activities, which require the use of private or collective transportation. Furthermore, the acquisition of addictions like smoking, the use of domestic PM generators (stoves and ovens), and the establishment of unhealthy lifestyles, increase the risk of developing chronic degenerative diseases [15]. Such pathological conditions can cause

disability and premature retirement. Moreover, these diseases share common features in the deepest changes at the molecular level like oxidative stress and chronic inflammation. This also applies to neurodegenerative diseases, which, at a late stage, lead to dementia, loss of personality, high economic expenses (caregivers and hospital), social conflicts, and patients becoming a heavy burden to relatives [49][50][51][52].

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