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Neurotoxicity of traffic-related air pollution

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ABSTRACT

The central nervous system is emerging as an important target for adverse health effects of air pollution, where it may contribute to neurodevelopmental and neurodegenerative disorders. Air pollution comprises several components, including particulate matter (PM) and ultrafine particulate matter (UFPM), gases, organic compounds, and metals. An important source of ambient PM and UFPM is represented by traffic-related air pollution, primarily diesel exhaust (DE). Human epidemiological studies and controlled animal studies have shown that exposure to air pollution, and to traffic-related air pollution or DE in particular, may lead to neurotoxicity. In particular, air pollution is emerging as a possible etiological factor in neurodevelopmental (*e.g.* autism spectrum disorders) and neurodegenerative (*e.g.* Alzheimer's disease) disorders. The most prominent effects caused by air pollution in both humans and animals are oxidative stress and neuro-inflammation. Studies in mice acutely exposed to DE (250–300 μg/m^3 for 6 h) have shown microglia activation, increased lipid peroxidation, and neuroinflammation in various brain regions, particularly the hippocampus and the olfactory bulb. An impairment of adult neurogenesis was also found. In most cases, the effects of DE were more pronounced in male mice, possibly because of lower antioxidant abilities due to lower expression of paraoxonase 2.

1. Introduction

Air pollution is a mixture of several components, including gases, organic compounds, metals, and ambient particulate matter (PM); the latter is believed to be the most widespread threat, and has been heavily implicated in disease (Moller et al., 2010; Costa et al., 2014a). PM is usually characterized by aerodynamic diameter: for example, PM_{10} is comprised of particles <10 μm in diameter, while $PM_{2.5}$ represents particles <2.5 μm in diameter. Also of relevance are ultrafine PM (UFPM, with diameter <100 nM), which may easily reach the general circulation and distribute to various organs including the brain (Oberdoerster et al., 2002; Genc et al., 2012). UFPM can also access the brain through the nasal olfactory mucosa, reaching first the olfactory bulb (Oberdoerster et al., 2002; 2004; Peters et al., 2006). The populations of many countries, particularly in South and East Asia, are often exposed to relatively high levels of PM (≥100 μg/m^3) (Brook et al., 2010; Van Donkelaar et al., 2015). Table 1 shows (as an illustrative example) the levels of $PM_{2.5}$ measured on two randomly chosen days in thirteen cities worldwide; in certain cities in India or China, but also in Peru, maximum levels of $PM_{2.5}$ are often above 100 μg/m^3.

Traffic-related air pollution is a major contributor to global air pollution, and diesel exhaust (DE) is its most important component (Ghio et al., 2012). DE contains more than 40 toxic air pollutants, and is a major contributor to ambient PM, particularly of fine ($PM_{2.5}$) and ultrafine PM (USEPA, 2002). DE exposure is often utilized as a measure of traffic-related air pollution. Diesel engines provide power to a wide range of vehicles, heavy equipment, and other machinery utilized in numerous industries, including transportation, construction, agriculture, railroad, maritime, mining and various types of manufacturing operations. Several million workers in the U.S.A. are exposed to diesel exhaust (DE) either occasionally or on a prolonged basis. Such occupational exposures to DE-PM can also be quite high, often exceeding 200–300 μg/m^3 in bus garage, construction and dock workers, with miners experiencing the highest exposures (up to 1000 μg/m^3) (Pronk et al., 2009).

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Table 1
Air pollution in selected cities worldwide.

City	$PM_{2.5}$ ($\mu g/m^3$)	
	June 10, 2015	September 13, 2015
Hyderabad, India	301	109
New Delhi, India	170	154
Zhengzhou, China	416	227
Bejing, China	215	126
Lima, Peru'	182	156
Seattle, WA, USA	51	52
New York, NY, USA	–	59
Los Angeles, CA, USA	–	68
Anchorage, AK, USA	42	38
Montreal, Quebec, Canada	47	47
London, Great Britain	–	70
Madrid, Spain	–	55
Paris, France	–	56

$PM_{2.5}$ (maximum level) measured on June 10 and on September 13, 2015 in the indicated cities. Days were selected at random, and cities were selected as examples to show high and low levels of $PM_{2.5}$. All information were found in http://aqicn.org/map/world.

The association between air pollution, particularly PM, and morbidity and mortality caused by respiratory and cardiovascular diseases is well established (Brook and Rajagopalan, 2007; Gill et al., 2011). Such peripheral toxicities are believed to be caused by oxidative stress and inflammatory processes (Brook et al., 2010; Lodovici and Bigagli, 2011; Anderson et al., 2012). Increased oxidative stress and inflammation have also been shown following exposure of rodents to DE (Weldy et al., 2012; Yin et al., 2013). In the case of DE exposure, a potential increase in lung tumors has also been suggested (Benbrahim-Tallaa et al., 2012).

2. Neurotoxicity of air pollution: epidemiological and experimental evidence

In recent years evidence has been accumulating from human epidemiological and animal studies, suggesting that air pollution may negatively affect the central nervous system (CNS) and contribute to CNS diseases (Calderon-Garciduenas et al., 2002; Block and Calderon-Garciduenas, 2009; Genc et al., 2012; Block et al., 2012). $PM_{2.5}$ and UFPM are of much concern in this regard, as these particles can enter the circulation and distribute to various organs, including the brain (Oberdoerster et al., 2002; 2004; Genc et al., 2012), in addition to gaining direct access to the brain through the nasal olfactory mucosa (Oberdoerster et al., 2004; Peters et al., 2006; Lucchini et al., 2012; Garcia et al., 2015). Decreased cognitive function, olfactory dysfunction, auditory deficits, depressive symptoms and other adverse neuropsychological effects have been reported in humans (Ranft et al., 2009; Freire et al., 2010; Calderon-Garciduenas et al., 2010, 2011; Fonken et al., 2011; Guxens and Sunyer, 2012). In addition, a controlled acute exposure to DE (300 $\mu g/m^3$, 1.2×10^6 suspended particles/cm^3, for 1 h) has been shown to induce EEG changes (Crüts et al., 2008). In highly exposed individuals, post-mortem investigations have revealed increased markers of oxidative stress and neuroinflammation (Calderon-Garciduenas et al., 2008, 2011, 2012; Levesque et al., 2011a).

Animal studies corroborate the human observations (Costa et al., 2014a). For example, dogs exposed to heavy air pollution presented evidence of chronic inflammation and neurodegeneration in various brain regions (Calderon-Garciduenas et al., 2002, 2003), and mice exposed to traffic in a highway tunnel had higher levels of pro-inflammatory cytokines in brain (Bos et al., 2012). Controlled exposure to DE has been reported to alter motor activity, spatial learning and memory, novel object recognition ability, and emotional behavior and to cause oxidative stress and neuro-inflammation in the CNS (MohanKumar et al., 2008; Gerlofs-Nijland et al., 2010; Win-Shwe and Fujimaki, 2011; Levesque et al., 2011b). Additionally, in our laboratory, we have carried out a series of studies in mice that indicate how even an acute exposure to DE (250–300 $\mu g/m^3$ for 6 h) causes oxidative stress, microglia activation, and neuro-inflammation, and impairs neurogenesis in various brain regions (see following section).

3. Acute diesel exhaust exposure in mice: factors affecting neurotoxicity

Our current studies are investigating neurotoxic effects of DE exposure in both adult and developing mice. Adult mice (8 weeks of age) were exposed for 6 h to filtered air (FA) or to 250–300 $\mu g/m^3$ DE. DE was derived from a Yanmar YDG5500 diesel generator, with load maintained at 75% of rated capacity, using No. 2 undyed, on-highway fuel and Royal Purple Duralec 15W-40 Synthetic crankcase oil. During exposures, DE concentrations were continuously measured and maintained at steady concentrations using a feedback controller monitoring fine particulate levels (Gould et al., 2008; Fox et al., 2015). DE was composed of $PM_{2.5}$ or smaller, with a mean aerodynamic diameter of 100 nm. At the end of the exposure, oxidative stress was assessed in brain regions by measuring lipid peroxidation, and a number of pro-inflammatory cytokines (IL-1α, IL-1β, IL-3, IL-6, TNF-α) were measured in the olfactory bulb and the hippocampus. DE caused a significant increase in lipid peroxidation in all brain regions; levels of pro-inflammatory cytokines were also increased, while the anti-apoptotic cytokine IL-9 was decreased (Giordano et al., 2013a; Cole et al., unpublished results). Some findings of these studies (which will be fully published elsewhere) are shown in Tables 2 and 3. Mice exposed to DE as described had significant higher levels of lipid peroxidation and of the pro-inflammatory cytokine TNF-α (tumor necrosis factor-α) than mice exposed to filtered air. DE exposure also caused microglia activation, as assessed by measuring levels of Iba1 (ionized calcium binding adaptor molecule 1) by Western blot and immunocytochemistry, and by measuring binding of TSPO (translocator protein) in various brain regions (Cole et al., unpublished results). As brain inflammation has been reported to inhibit adult neurogenesis (Ekdahl et al., 2003), we also investigated whether acute DE exposure would result in decreased adult neurogenesis in the hippocampal subgranular zone (SGZ) and the subventricular zone (SVZ), using the BrdU/NeuN co-localization method (Coburn et al., 2015; Coburn et al., unpublished results). DE exposure caused a significant decrease in neurogenesis in both brain regions (see Table 4 for findings in the SGZ).

As indicated earlier (Costa et al., 2014a), susceptibility to air pollution neurotoxicity can be modulated by a number of factors, including sex, genetic background and age. Sex is a variable which

Table 2
Gender differences in susceptibility to the effects of DE in the hippocampus.

End-point/Sex	FA	DE
MDA (nmol/g)		
Male	4.7 ± 0.2	$13.3 \pm 0.3^{**}$
Female	$2.2 \pm 0.1^{\#}$	$4.2 \pm 0.3^{**\#}$
TNF-α (pg/ml)		
Male	1.4 ± 0.4	$9.8 \pm 1.9^{**}$
Female	0.7 ± 0.1	$1.7 \pm 0.2^{*}$

Male and female mice were exposed to DE (250–300 $\mu g/m^3$) or filtered air (FA) for 6 h. Levels of malonyldialdehyde (MDA) and of tumor necrosis factor-α (TNF-α) were measured in the hippocampus as markers of oxidative stress (lipid peroxidation) and of neuro-inflammation, respectively. Results represent the mean (± SE) of three animals/group. Significantly different from FA, $^{*}p < 0.05$; $^{**}p < 0.01$; significantly different from male, $^{\#}p < 0.05$ (two-way ANOVA followed by Bonferroni test for multiple comparisons). *Source:* Costa et al. (2014a).