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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 six hours) have shown microglia activation, increased lipid peroxidation, and neuro-inflammation 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.

Keywords

Traffic-related air pollution; Diesel exhaust; Neurotoxicity; Oxidative stress; Neuro-inflammation; Neurodevelopmental disorders; Neurodegenerative diseases

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

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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 (Oberdoester et al. 2002; Genc et al. 2012). UFPM can also access the brain through the nasal olfactory mucosa, reaching first the olfactory bulb (Oberdoester 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 $\mu g/m^3$) (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 $\mu g/m^3$.

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 $\mu g/m^3$ in bus garage, construction and dock workers, with miners experiencing the highest exposures (up to 1000 $\mu g/m^3$) (Pronk et al. 2009).

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).

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 μg/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 μg/m^3 for 6 h) causes oxidative stress, microglia activation, and neuro-inflammation, and impairs neurogenesis in various brain regions (see following section).

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 μg/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. in preparation). 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., in preparation). 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. in preparation). 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 deserves further investigations (Clougherty, 2010), as information so far is very limited. We had previously proposed that sex differences in susceptibility to neurotoxicity induced by traffic-related air pollution may indeed exist, and that these may be associated to the differential expression of the antioxidant/anti-inflammatory enzyme paraoxonase 2 (PON2) in brain from male and females (Giordano et al. 2013b; Costa et al. 2014b). PON2 is an intracellular enzyme, capable of scavenging reactive oxygen species and thereby protecting cells from oxidative stress-induced neurotoxicity, in addition to have anti-inflammatory properties (Costa et al. 2014b).In all brain regions and cell types studied, and in several species including humans, PON2 levels are higher in females than in males, and levels of PON2 inversely correlate with the degree of susceptibility to the *in vitro* toxicity of neurotoxicants causing oxidative stress (Giordano et al. 2013a). As shown in Table 2, sex differences also exist with regard to susceptibility to DE-induced lipid peroxidation and neuroinflammation *in vivo* (Giordano et al. 2013b; Costa et al. 2014a). Indeed acute DE exposure (250 μg/m^3 for 6 h) increased levels by malondialdehyde in hippocampus by 2.8-fold in male mice and only 1.9-fold in female animals. Furthermore, levels of TNF-α in hippocampus increased by 7-fold in male and 2.4-fold in female mice (Table 2). Sex differences were also observed with regard to the effect of acute DE exposure on adult neurogenesis. In the SGZ, higher levels of neurogenesis were observed in control male mice (Table 4), confirming previous observations (Koutseff et al. 2014). In all animals a significant decrease of neurogenesis was found, which was more pronounced in female mice. As air pollution may be involved in the etiology of neurodevelopmental and neurodegenerative diseases such as autism and Parkinson's disease, whose incidence is higher in males (van den Edeen et al. 2003; Schaafsma and Pfaff, 2014), such sex differences in susceptibility should be further substantiated and characterized.

Given the overall relevance of gene-environment interactions in toxicology and risk assessment (Costa and Eaton, 2006), the possibility that genetic polymorphisms may affect susceptibility to air pollution-induced neurotoxicity should also be considered. Because oxidative stress is a preponderant response to DE exposure, we hypothesized that genetically-based deficiencies in antioxidant defense mechanisms may exacerbate DE neurotoxicity. To test this hypothesis we utilized the *Gclm* mouse, which lacks the modifier subunit of glutamate-cysteine ligase, the first and rate-limiting enzyme in the synthesis of glutathione (GSH), a main player in cellular defense against oxidative stress. *Gclm*$^{-/-}$ mice have very low levels of GSH in all tissues including the brain (Giordano et al. 2006), though they may up-regulate other antioxidant pathways; in contrast, *Gclm*$^{+/-}$ mice have only moderate reductions in GSH but may more closely resemble an human polymorphism of *Gclm* (Nakamura et al. 2002). We thus hypothesized that *Gclm*$^{-/-}$ mice would be more susceptible to DE neurotoxicity than wildtype mice, and *Gclm* heterozygotes may be even more susceptible. Results shown in Table 3 with regard to a single brain region, the olfactory bulb, support this hypothesis. *Gclm*$^{-/-}$ mice are indeed more sensitive than wild-type mice (*Gclm*$^{+/+}$) to oxidative stress (lipid peroxidation) and neuro-inflammation (levels of the pro-inflammatory cytokine interleukin-1β) induced by acute DE exposure (250-300 μg/m^3 for 6 h). Furthermore, heterozygote mice (*Gclm*$^{+/-}$) showed the highest sensitivity to DE

neurotoxicity (Table 3). The latter findings confirm a previous observation of enhanced lung inflammation in *Gclm*$^{+/-}$ mice upon exposure to DE (Weldy et al. 2012). As there are several genetic polymorphisms of enzymes involved in oxidative stress and neuro-inflammation, the possibility of genetically-based susceptibility to air pollution neurotoxicity would warrant further investigations.

Air pollution as a risk factor for neurodevelopmental and neurodegenerative diseases

In addition to gender and genetic background, age is emerging as an important determinant for susceptibility to air pollution neurotoxicity, and there is much interest in the role that traffic-related air pollution may play in the etiology of neurodevelopmental and neurodegenerative diseases.

Developmental neurotoxicity of air pollution

Epidemiological and animal studies suggest that young individuals may be particularly susceptible to air pollution-induced neurotoxicity (Calderon-Garciduenas et al. 2008; 2011; 2012; Freire et al. 2010; Guxens and Sunjer, 2012; Guxens et al. 2014). Studies in Mexico City have revealed elevated levels of neuro-inflammatory markers in brain of children exposed to high air pollution, as well as cognitive deficits (Calderon-Garciduenas et al. 2008; 2011; 2013). Newman et al. (2013) reported hyperactivity in 7-year old children associated with early life exposure to traffic-related air pollution. In six European cohorts, exposure to air pollution during pregnancy was found to be associated with delayed psychomotor development (Guxens et al. 2014). Recent studies reported that exposure to traffic-related air pollution is inversely associated with sustained attention in adolescents (Kicinski et al. 2015), and to lower cognitive development in primary school children (Sunyer et al. 2015). Experimental studies also indicate that developmental exposure to DE may cause neurotoxicity (Ema et al. 2013). *In utero* exposure to high levels of DE (1.0 mg/m^3) caused alterations in motor activity, motor coordination and impulsive behavior in male mice (Yokota et al. 2009; 2013; Suzuki et al. 2010). Early postnatal exposure of mice to concentrated ambient PM was reported to cause behavioral changes (enhanced bias towards immediate rewards), as well as long-term impairment of short term memory and impulsivity-like behavior (Allen et al. 2013; 2014a). Depression-like responses were found in mice exposed prenatally to urban air nanoparticles (Davis et al. 2013). Additional studies have shown that developmental DE exposure of mice alters motor activity, spatial learning and memory, and novel object recognition ability, and causes changes in gene expression, neuro-inflammation, and oxidative damage (Hougaard et al. 2008; 2009; Tsukue et al. 2009; Win-Shwe et al. 2008; 2014).

Among neurodevelopmental disorders that may be associated with air pollution, much attention has been devoted to autism, and a number of recent studies have indeed found associations between exposures to traffic-related air pollution and this syndrome. Autism is a neurodevelopmental disorder characterized by marked reduction of social and communicative skills, and by the presence of stereotyped behaviors (Levy et al. 2009), and the term autism spectrum disorders (ASD) is usually utilized to include autism and a range

of similar disorders. The symptoms of ASD are typically present before the age of three, and are often accompanied by abnormalities of cognitive functioning, learning, attention, and sensory processing (Levy et al. 2009). The incidence of ASD appears to have increased in the past few decades, and it is now estimated at about 7-9/1000, though certain studies have identified up to 27/1000 children affected by ASD (Boyle et al. 2011a; Wingate et al. 2012); ASD is also 4-12 times more common in males than in females (Schaafsma and Pfaff, 2014). The economic burden of caring for an individual with ASD and intellectual disability during his or her lifespan has been estimated at $2.4 million (Buescher et al. 2014). Increasing evidence indicates that children with ASD have higher levels of oxidative stress (Rose et al. 2012; Frustaci et al. 2012), as well as higher microglia activation, neuro-inflammation and increased systemic inflammation (Morgan et al. 2010; El-Ansary and Al-Ayadhi, 2012; Theoharides et al. 2013; Suzuki et al. 2013; Depino et al. 2013).

Two studies in California by Volk et al. (2011; 2013) found that residential proximity to freeways and gestational and early-life exposure to traffic-related air pollution were associated with autism (OR=1.86; 95% CI=1.04-3.45). Similar results were obtained in another epidemiological study in California (Becerra et al. 2013), and in the Nurses' Health Study II, in which perinatal DE exposure was significantly associated with ASD, particularly in boys (Roberts et al. 2013). An additional study of two cohorts in North Carolina and California also reported an association between PM exposure and ASD, particularly when exposure occurred in the third trimester of pregnancy (Kalkbrenner et al. 2015). The higher susceptibility of third trimester exposure was also evidenced by a study of Raz et al. (2015) in the Nurses' Health Study II cohort. The few available animal studies are in agreement with the human observations (Costa et al. 2014a). Prenatal and early life exposure of mice to DE is associated with a number of behaviors similar to those present in humans with ASD, including higher levels of motor activity, elevated levels of self-grooming, and increased rearing (Thirtamara Rajamani et al. 2013). Postnatal exposure to concentrated ambient ultrafine particles caused persistent glial cell activation, various neurochemical changes and ventriculomegaly (lateral ventricular dilation), which occurred preferentially in male mice (Allen et al. 2014b), while prenatal exposure of mice to DE has been shown to disrupt DNA methylation in the brain, particularly affecting genes involved in neuronal differentiation and neurogenesis (Tachibana et al. 2015). In preliminary studies we found that prenatal exposure of mice to DE at environmentally relevant concentrations (250-300 $\mu g/m^3$, from gestational day (GD) 0 to GD 18) causes subtle behavioral effects in the domains relevant to ASD (Chang, Costa et al. unpublished). Specifically, we saw an increase in locomotor activity in DE-exposed mice (male only, $p<0.05$), a decreased performance in the rotarod test (both sexes, $p<0.05$), and an effect in the social novelty test (both sexes, $0.1>p>0.05$). However, as said, human studies have indicated that the association between PM exposure and ASD is stronger when exposure occurs in the third trimester of pregnancy (Kalkbrenner et al. 2015; Raz et al. 2015), which is equivalent to the first few postnatal weeks in mice or rats (Bayer et al. 1993). Ongoing studies are thus investigating behavioral effects of DE exposure encompassing both the prenatal and postnatal periods in mice, from GD 0 to postnatal day 21.

Air pollution and neurodegenerative disorders

In addition to an enhanced susceptibility of the developing brain, the aging brain may also be particularly susceptible to air pollution-induced neurotoxicity. First, many of the epidemiological studies identifying adverse effects of air pollution on behavior, particularly cognitive behavior, have identified significant effects in the elderly (Ranft et al. 2009; Power et al. 2011; Weuve et al. 2012; Chen et al. 2015). As said, primary mechanisms of adverse effects of air pollution in the CNS appear to be related to oxidative stress and neuro-inflammation. These processes are also involved in the etio-pathology of various neurodegenerative diseases (Teeling and Perry, 2009; Lee et al., 2010; Qian et al., 2010). Indeed, an increased incidence of neurodegenerative disease pathologies, namely increased beta-amyloid 42, hyper-phosphorylated tau, and increased alpha-synuclein, have been found upon exposure to high air pollution (Calderon-Garciduenas et al., 2004; 2008; 2012) or upon controlled DE exposure (Levesque et al., 2011a). Olfactory dysfunction is another important early symptom of neurodegenerative diseases, particularly of Parkinson's disease (Mesholam et al., 1998; Doty et al., 1987; Doty, 2012), in which damage to the olfactory bulb actually precedes neuropathology in the motor areas, such as substantia nigra and striatum (Braak et al., 2004); olfaction problems have also been reported in individuals exposed to heavy air pollution (Calderon-Garciduenas et al., 2010).

Conclusions and further studies

While the connection between air pollution and respiratory diseases was straightforward and easy to formulate, effects on the cardiovascular system have later emerged as most relevant (Gill et al. 2011). In the past decade or so, evidence has started to accumulate suggesting that the nervous system may be an important target for air pollution, and particularly for traffic-related air pollution, of which DE is a common surrogate. As pointed out before, there is a strong convergence between human epidemiological studies and experimental animal studies with regard to both behavioral and biochemical end-points affected by such exposures (Costa et al. 2014a). In addition, *in vitro* studies support *in vivo* observations by showing that DE-derived particles can activate microglia and induce oxidative stress and neuro-inflammation (Block et al. 2004; Levesque et al. 2011b; Roqué et al. 2015; Roqué et al., unpublished). Exposure to high levels of air pollution, as common in several locations around the world, is troublesome (see Table 1 as example), in light of the suggested associations between exposure and neurodevelopmental and neurodegenerative diseases, such as autism or dementia. In addition, given that even short-term exposures can elicit biochemical alterations associated with such diseases, occupational exposures in workplaces of generally low air pollution are also of concern. Measures to decrease emissions leading to poor air quality are the obvious first choice to pursue in the effort to protect human health. However, further studies aimed at better characterizing the effects of air pollution on the CNS, its underlying mechanisms, and its role in the etiology of neurodevelopmental and neurodegenerative diseases are certainly warranted. In particular, the possibility that sexes may be differentially affected by air pollution (Clougerty, 201) needs to be investigated, in light of the higher incidence of neurodevelopmental (e.g. ASD) and neurodegenerative (e.g. Parkinson's disease) disorders in males. Finally, gene-environment interactions still need to be investigated in the context of CNS and air pollution. Recent events, evidencing higher

emission from diesel engines than those indicated, have generated substantial concern, which need to be addressed by further investigations on DE adverse health effects.

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Highlights

- Traffic-related air pollution may cause neurotoxicity
- Traffic-related air pollution may contribute to neurodevelopmental and neurodegenerative disorders
- Particulate matter (PM) from diesel exhaust can cause oxidative stress and neuroinflammation

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 $PM_{2.5}$. Al information were found in http://aqicn.org/map/world

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 ± 0.3 **
Female	2.2 ± 0.1 #	4.2 ± 0.3 *#
TNF-α (pg/ml)		
Male	1.4 ± 0.4	9.8 ± 1.9 **
Female	0.7 ± 0.1	1.7 ± 0.2 *#

Male and female mice were exposed to DE (250-300 μg/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).

Table 3

Modulation of DE neurotoxicity in the olfactory bulb by glutathione levels

End-point	*Gclm*	FA	DE
MDA (nmol/g)	+/+	5.7 ± 0.2	21.2 ± 0.3**
	-/-	5.2 ± 0.3	35.4 ± 0.3**#
	+/-	9.7 ± 1.0	45.0 ± 0.7**#
IL-1β (pg/ml)	+/+	12.7 ± 1.6	31.1 ± 6.1**
	-/-	7.2 ± 0.3	42.6 ± 2.4**
	+/-	18.6 ± 0.7	78.5 ± 4.3**#

Male mice were exposed to DE (250-300 μg/m^3) or filtered air (FA) for 6 h. Levels of malonyldialdehyde (MDA) and of interleukin-1beta (IL-1β) were measured in the olfactory bulb 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,

** $p<0.01$; significantly different from *Gclm*$^{+/+}$,

# $p<0.05$ (two-way ANOVA followed by Bonferroni test for multiple comparisons). Source: Costa et al (2014).

Table 4

Effect of diesel exhaust exposure on adult hippocampal neurogenesis

Treatment	Male	Female
	(BrdU$^+$, NeuN$^+$/BrdU$^+$)	
FA	0.73 ± 0.05	0.41 ± 0.06$^{\#}$
DE	0.21 ± 0.03***	0.22 ± 0.02*

Neurogenesis in the hippocampal subgranular zone of male and female mice exposed for 6 h to diesel exhaust (DE; 250-300 μg/m^3) or filtered air (FA). Data are expressed as the ratio of cells labeled with BrdU (brmodeoxyuridine) and NeuN (a neuronal marker) over cells labeled with BrdU. Results represent the mean (± SE) of three animals/group. Significantly different from FA,

*p<0.05;

***p<0.001; significantly different from male,

$^{\#}$p<0.05 (two-way ANOVA followed by Bonferroni test for multiple comparisons). Source: Coburn et al. (2015).