Available online at www.sciencedirect.com
ScienceDirect
NeuroToxicology 29 (2008) 479–488
NeuroToxicology

Particulate matter, oxidative stress and neurotoxicity

Sheba M.J. MohanKumar [a], Arezoo Campbell [b], Michelle Block [c], Bellina Veronesi [d,*]

[a] Department of Pharmacology and Toxicology, Michigan State University, E. Lansing, MI, United States
[b] Department of Pharmaceutical Sciences, Western University of Health Sciences, Pomona, CA, United States
[c] Department of Anatomy and Neurobiology, Virginia Commonwealth University Medical Campus, Richmond, VA, United States
[d] Neurotoxicology Division, National Health and Environmental Effects Research Laboratory, US Environmental Protection Agency, Research Triangle Park, NC, United States

Received 27 November 2007; accepted 12 December 2007
Available online 4 January 2008

Abstract

Particulate matter (PM), a component of air pollution has been epidemiologically associated with sudden deaths, cardiovascular and respiratory illnesses. The effects are more pronounced in patients with pre-existing conditions such as asthma, diabetes or obstructive pulmonary disorders. Clinical and experimental studies have historically focused on the cardiopulmonary effects of PM. However, since PM particles carry numerous biocontaminants that are capable of triggering free radical production and cytokine release, the possibility that PM may affect organs systems sensitive to oxidative stress must be considered. Four independent studies that summarize the neurochemical and neuropathological changes found in the brains of PM exposed animals are described here. These were recently presented at two 2007 symposia sponsored by the Society of Toxicology (Charlotte, NC) and the International Neurotoxicology Association (Monterey, CA).

Keywords: Particulate matter; Oxidative stress; Innate immunity; Neurotoxicity; Mac-1; HPA axis

1. Introduction

Incidences of neurodegenerative diseases are increasing within the population (Di Monte et al., 2002; Strong, 2004; Elbaz et al., 2007; Tansey et al., 2007) raising the possibility that environmental exposures, combined with susceptibility factors (e.g., genetics, diseased states, malnutrition, etc.) contribute to these increases. This section discusses the possibility that air pollution is an important environmental risk factor. Particulate matter (PM), a component of air pollution, has been epidemiologically associated with sudden deaths in the elderly and respiratory distress in sensitive individuals (Brook and Rajagopalan, 2007; Goldberg et al., 2006). Its effects are especially debilitating to those with pre-existing respiratory conditions such as asthmatics, smokers, diabetics, pregnant women and individuals with cardiac obstructive pulmonary disorders. PM particles are covered with biocontaminants (e.g., endotoxins, mold and pollen) and convey free radical activity which can damage the lipids, nucleic acids, and proteins of target cells on contact and stimulate inflammatory cytokine release. Although, the historical focus of PM toxicity has been cardiopulmonary targets, it is now appreciated that inhaled nano-size (<100 nm) PM particles quickly exit the lungs and enter the circulation where they distribute to various organ systems (i.e., liver, kidneys, testes and lymph nodes) (Kreyling et al., 2002; Oberdorster et al., 2004; Takenaka et al., 2001). Damage to these secondary targets occurs though oxidative stress pathways (Cordier et al., 2004; Samet et al., 2004; Pohjola et al., 2003).

The brain is vulnerable to oxidative stress damage because of its high energy use, low levels of endogenous scavengers (e.g., vitamin C, catalase, superoxide dismutase etc.), high metabolic demands, extensive axonal and dendritic networks, and high cellular content of lipids and proteins (Mattson, 2001). The possibility that the brain might also be targeted by PM was first raised in a 2002 editorial (Oberdorster and Utell, 2002) and followed by reports showing that nanosize particles could cross

* Corresponding author. Tel.: +1 919 541 5780.
E-mail addresses: mohankumrs@cvm.msu.edu (S.M.J. MohanKumar), acampbell@westernu.edu (A. Campbell), MBlock@vcu.edu (M. Block), veronesi.bellina@epa.gov (B. Veronesi).

0161-813X/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuro.2007.12.004

the blood brain barrier (BBB) (Lockman et al., 2004) and physically enter the central nervous system (CNS) of animals in small numbers (Kreyling et al., 2002).

The following studies were conducted by Sheba MohanKumar in collaboration with J.R. Harkema and P.S. MohanKumar and examined PM's effect on brain neurotransmitters and stress axis activity. PM exposure increases the risk for allergic airway diseases (e.g., asthma and bronchitis) (Kleinman et al., 2007) and predisposes susceptible populations to increased risk for cardiovascular disease (Bhatnagar, 2006). Sub-chronic exposure to diesel exhaust, vehicle emmisions and other types of air pollution have been associated with higher levels of the stress hormone, cortisol (Ising et al., 2004; Tomei et al., 2003). The common factor in both cardiovascular disorders and allergic airway disease is physiological stress. Although there are no data directly linking the stress axis to cardiovascular disease and air pollution, physiological stress is thought to play a major role since both emotional stress and immune stress increase the risk for cardiovascular disease (Hassan et al., 2007; Knuefermann et al., 2004). The hypothalamo–pituitary–adrenal axis (HPA) or ''stress axis'' houses neurons which contain corticotrophin releasing hormone (CRH). CRH neurons contribute to activation of the stress axis and are largely located within the paraventricular nucleus (PVN) of the hypothalamus. Their terminals extend to the median eminence where CRH is released and enters the portal circulation to reach the anterior pituitary. Here it stimulates corticotrophs to secrete adrenocorticotrophic hormone (ACTH) which in turn enters the general circulation and acts on the adrenal glands to increase the secretion of the stress hormone, cortisol, in humans and corticosteroids, in the laboratory rat. Several neurotransmitters act at the level of the hypothalamus to increase the secretion of CRH and increase stress axis activity (Muller and Nistico, 1988). The catecholamine, norepinephrine (NE) appears to stimulate CRH secretion and increase HPA activity (MohanKumar and MohanKumar, 2005; MohanKumar et al., 1998; Pacak et al., 1995). Transection of noradrenergic fibers that innervate the PVN reduces both NE levels and HPA activation. (Szafarczyk et al., 1987). Noradrenergic antagonists can also decrease HPA activity (Muller and Nistico, 1988). Together, these data indicate that NE has a positive influence on the stress axis.

In view of these relationships, the following experiment was designed to examine the relationship between physiological stress and PM air pollution. The effects of PM on NE levels of the PVN were studied in normal rats and those with preexisting allergic airway disease to test the hypothesis that the presence of existing airway disease would aggravate PM's effect on the stress axis. Adult male Brown Norway rats ($n = 8$/group) were instilled intranasally with ovalbumin (OVA) or saline. Two weeks later they were again treated with OVA or saline and then exposed to concentrated air particles (CAPs) generated from an urban community (Grand Rapids, Michigan) using a mobile air research laboratory (AirCARE 1). Animals were exposed to CAPs (500 $\mu g/m^3$; 2.5 μm aerodynamic diameter) for 1 d or 3 d (8 h/d) and sacrificed 24 h post-exposure. Their brains were removed and the PVN of the hypothalamus microdissected. Concentrations of aminergic neurotransmitters and their metabolites were measured using high-performance liquid chromatography with electrochemical detection. Serum from trunk blood was analyzed for corticosterone concentrations using radioimmunoassay (Sirivelu et al., 2006).

Concentrations of NE levels found in the PVN were comparably elevated in normal animals exposed to CAPs (12.45 ± 2.7 pg/μg protein) and air exposed OVA pretreated animals (15.84 ± 2.8 pg/μg protein). However, NE levels were greatly stimulated in the PVN of CAPs exposed OVA-sensitized animals (19.06 ± 3.8 pg/μg protein) (Table 1). The effect of PM on serum corticosterone levels was also studied in normal and OVA-sensitized animals exposed to CAPs by inhalation or to saline intranasally. After 2 weeks, these animals were exposed to OVA/saline prior to CAPs exposure for 1 or 3 d. Significant differences ($p < 0.05$) in serum corticosterone levels were noted in both the 1 and 3 d exposures. Serum corticosterone was significantly elevated in the OVA + CAPs group (242.786 ± 33.315 ng/ml) relative to CAPs exposed saline animals (114.55 ± 20.9 ng/ml). The corticosterone levels in CAPs-exposed saline animals were significantly higher than those of air-saline exposed animals (56.01 ± 10.2). These data indicate that while allergic airway disease by itself is capable of stimulating the stress axis, exposure to CAPs aggravates this condition and suggests that the pre-existence of allergic airway disease increases the sensitivity to these effects. These effects were confined to the PVN and not seen in other areas of the hypothalamus indicating that the neurotransmitter changes were highly region specific. The effects are time-dependent since exposure to CAPs for 1 d in increases both NE levels in the PVN and exposure. When the exposure was prolonged to 3 d, the level of stress axis activity was altered indicating that the stress responses were duration specific (Sirivelu et al., 2006).

Table 1
Effects of CAPs on NE levels in the PVN and serum corticosterone after 1 and 3 d exposure

Parameters	Air + saline (d)		Air + ovalbumin (d)		CAPs + saline (d)		CAPs + ovalbumin (d)	
	1	3	1	3	1	3	1	3
Norepinephine (pg/μg protein)	8.896 ± 1.09	$14.25 \pm 0.48^{\dagger}$	15.839 ± 2.85*	15.569 ± 1.13	12.453 ± 2.72*	14.42 ± 0.69	19.056 ± 3.8*	13.501 ± 0.72
Corticosterone (ng/ml)	56.096 ± 10.2	$164.87 \pm 2.84^{\dagger}$	294.04 ± 26.23*	192.84 ± 24.1	114.55 ± 20.9*	$174.31 \pm 16.62^{\dagger}$	242.79 ± 33.32*	194.29 ± 24.16

$^{\dagger}p < 0.05$ when compared to the corresponding values for 1 d exposure and *$p < 0.05$ when compared to different treatments within the same duration of exposure.