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Chronic Ill Effects of Air Pollution in Children: Neurological Derailment

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Introduction

I. Backround

A complex mixture of gases, particulate matter (PM), and chemicals present in outdoor and indoor air produces adverse health effects. Because the nasal cavity is a common portal of entry for such pollutants, the nasal olfactory and respiratory mucosa are vulnerable to damage and well-known targets for air pollutant-induced toxicity and carcinogenicity (Henriksson J & Tj¨alve H, 2000 and Morgan KT & Monticello TM , 1990). The nose-brain barrier depends on intact epithelia, including tight junctions and an intact xenobiotic metabolizing capacity (Dahl AR & Lewis JL, 1993). Olfactory receptor cell dendrites are in direct contact with the environment, and, thus, pinocytosis and neuronal transport are likely routes of access to the central nervous system (CNS) of potential toxins (Lin DM & Ngai J, 1999). Olfactory receptor neurons project from the sensory epithelium to targets within the olfactory bulb, the first synaptic relay in the olfactory pathway (Lin DM & Ngai J, 1999). The mucociliary apparatus of the respiratory mucosa also functions as a barrier to protect against neuronal uptake and transport by trapping insoluble inhaled material in a layer of secretions that are in continuous movement towards the nasopharynx (Morgan KT & Monticello TM, 1990). The contribution of air-pollutant exposure to airway epithelial injury is well documented. Healthy children and adult populations in Southwest Metropolitan Mexico City (SWMMC)—an urban area characterized by significant daily concentrations of pollutants such as ozone, PM, and aldehydes—have shown extensive damage to the respiratory nasal epithelium (Kelly FJ, 2004 and Calder ´on-Garcidue˜nas L, Rodr´õ guez-Alcaraz A, Villarreal-Calder ´on A, Lyght O & Janszen D, Morgan KT, 1998). Children in SWMMC display ultra structural evidence of deficiencies in nasal epithelial junction integrity, cytoplasmic deposition of PM, and altered mucociliary defense mechanisms (Calder ´on-Garcidue˜nas L, et al. 2001a). Canines living in SWMMC exhibit similar nasal respiratory lesions, along with respiratory bronchiolar and myocardial pathology (Calder ´on-Garcidue˜nas L, Mora-Tiscare˜no A, Chung CJ, Valencia G,Fordham LA, Garcia R, Osnaya N, Romero L, Acu˜na H, Villarreal-Calder ´on A, Devlin RB, Koren HS, 2000 and Calder ´on-Garcidue˜nas L, et al. 2001b). A sustained pulmonary inflammatory process is clearly seen in exposed canines (Calder ´on-Garcidue˜nas L, et al., 2001c) and SWMMC children show radiological and spirometric evidence of lung damage and cytokine imbalance (Calder ´on-Garcidue˜nas L, et al. 2001d). Impaired olfaction, hyposmia, or anosmia are important early changes in neurodegenerative diseases including Alzheimer's (AD) and Parkinson's disease (PD) (Hock C, Golombowski S, Muller-Spahn F, Peschel O, Riederer A, Probst A, Mandelkow E & Unger J, 1998; Kovacs T, Cairns NJ & Lantos PL, 1999, and Wszolek ZK & Markopoulou K, 1998), as well as in aging (Hirai T, Kojima S, Shimada A, Umemura T, Sakai M & Itakura C , 1996 and Hoffman HJ, Ishii EK & MacTurk RH, 1998). All layers of the olfactory bulb are affected in aging and AD, and olfaction is impaired in the early stages of AD Among the groups of environmental chemicals for which neurodevelopmental and neurobehavioural effects in children are to some extent documented are some heavy metals and polyhalogenated romatic hydrocarbons (PHAHs). The former primarily include

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lead, mercury and (less frequently) manganese, whereas, the most extensively studied PHAH species include the polychlorinated biphenyls (PCBs).

Ambient air pollution is a global health problem and it is an important factor associated with morbidity and mortality worldwide (Narayan, Ali et al. 2010). In high income countries air pollution was associated with 2.5% of all deaths, making it the eighth leading risk factor for mortality (Narayan, Ali et al. 2010). Pollutants do not stay within the national borders. They are carried by winds, contaminating water and soil far from their origin. The great London smog of 1952 focussed the world's attention on the problem of air pollution (LOGAN 1953). Since then there has been an improvement in air quality in developed countries, but a in developing countries air pollution continues to be a big problem. The air quality in large cities in developing countries is remarkably poor and large numbers of people living in these cities are exposed to levels of air pollutants well above the World Health Organization guidelines for air quality (Kim, 2004).

Traffic-related air pollution, basically urban outdoor pollution is a global public health problem. Cardio-respiratory effects and mechanisms have been fully investigated. In contrast, little is known regarding neurological effects, with only some preliminary evidence. In rats, ultrafine carbon particles have been found in the olfactory bulb and the cerebrum and cerebellum after inhalation exposure, his finding has been reproduced more recently with manganese particles directly translocated to the olfactory nerve from the nose to the brain. In one study, dogs living in a highly polluted region in Mexico City (Mexico) had an increase in brain inflammation compared with animals living in a less polluted area (Calder ´on-Garcidue˜nas L, Azzarelli B, Acuna H, et al. 2002). The brain tissue of animals from Mexico City had higher levels of nuclear factor-k Bactivation and nitric oxide production, as well as the principal pro-inflammatory cytokines interleukin (IL)-1 and tumour necrosis factor (TNF)-a, compared with the animals from the non polluted area (Campbell A, Oldham M, Becaria A, et al. 2005). In a study on human autopsies in Mexico City, exposure to severe air pollution has been associated with increased levels of cyclooxygenase (COX)-2 and accumulation of the 42-amino-acid form of β-amyloid, a cause of neuronal dysfunction (Caldero´n-Garciduen˜ as L, Reed W, Maronpot RR, et al. 2004).

Although urban air pollution crosses geographical and socio-economical boundaries, urban minority populations are likely to be more exposed to indoor and outdoor air pollution than other populations (Breysse, Buckley et al. 2005). Also, children may have increased exposures to air pollutants compared to adults, because of higher minute ventilation and higher levels of physical activity. They are also more exposed to ambient air pollution, because they usually spend much more time outdoors than adults (Kim, 2004).

II. Air Pollution

Pollutants are substances in the air that can cause harm to humans and the environment. They arise in different forms like gasses, solid particles and liquid droplets. They can also divided in pollutants from natural sources in the environment, like volcanism and forest fires (when started by lightning) and pollutants that are man-made or anthropogenic, like fossil fuel combustion emitted by traffic, power generation and industry. Both the natural and anthropogenic pollutants can also be classified as either primary or secondary pollutants. Primary pollutants are directly formed and emitted, whereas secondary pollutants are formed in the atmosphere, when primary pollutants react or interact. Since a lot of air pollutants are emitted by natural sources, industry and traffic, it is logical that people are mainly focused on the outdoor air pollution. However, it is important to realize that indoor air pollution (IAP) might also play a role in the origin of neurological effects. Especially in developing countries, most people still rely on solid fuels for cooking and heating, which generates high levels of pollutants like particulate matters and carbon-monoxide. Women and young children may be significantly more exposed to this form of air pollution because of their traditional role in the house hold. But also in developing countries IAP plays a role, since people tend to spend 80-90% of their time indoors and good ventilation is often lacking.

In this review we will mainly focus on the neurological effects of ambient air pollution. Toxicological studies will give an indication of the possible effects the air pollutants can have on the neurological development, whereas case studies will give insight into the extension of these effects in children.

a) Pollutants of Interest

i. *Particulate matter*

One of the most important groups of primary pollutants is the group of fine particles, also known as particulate matter (PM). This PM contains particles from different sizes, sources and chemical composition. Based on size, they are divided in three categories. Particles indicated by PM10 have a aerodynamic diameter of less than 10 μm. PM2.5 are particles smaller than 2.5 μm and PM0.1 are the particles smaller than0.1 which are also called ultra-fine particles (Miyata, van Eeden, 2011). Because of their size, the largest particles (2.5-10 μm) are not able to penetrate the respiratory tract very deeply. They are mainly deposited in the nasal cavity, larynx and trachea (Heyder, 2004). The particles that are between 0.1 and 2.5 μm penetrate the bronchi and bronchioles. However, the larger particles in this

group will still deposit mostly in the upper airway, whereas the particles between 0.1 and 1 μm hardly deposit at all (NRPB, 2004). The ultrafine particles (<0.1 μm) are able to penetrate the alveoli and have a deposition rate of more than 80% (NRPB). The origin of particulate matter can be natural (volcanoes, dust storms and forest fires), but mostly they are emitted as a result of fuel combustion from traffic and industry or agriculture.

ii. *Nitrogen dioxide & Ozone*

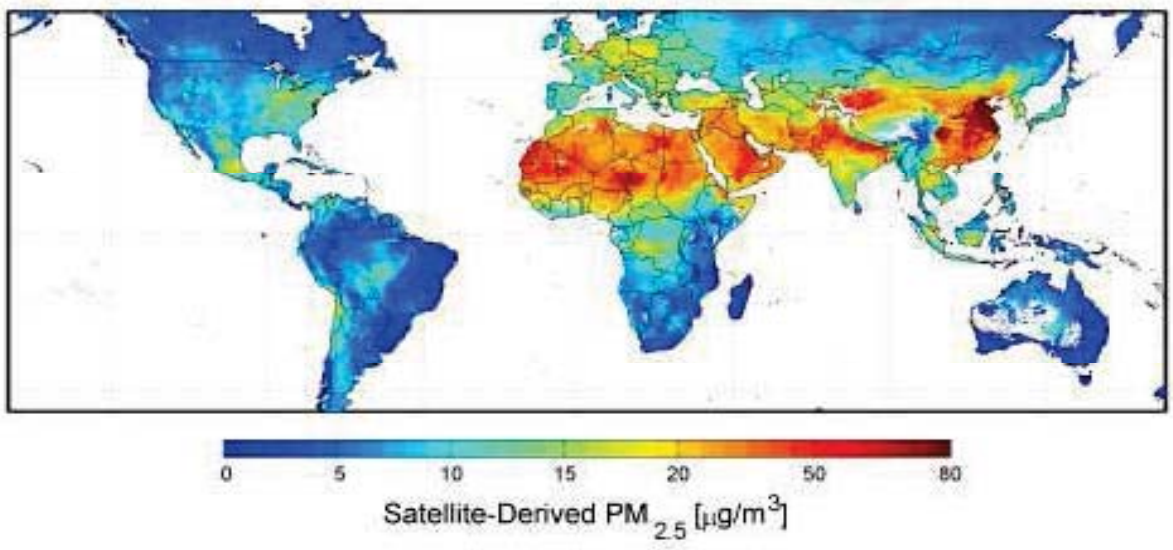
Nitrogen dioxide (NO_2) is formed in most combustion processes that use oxygen as an oxidant. NO2 is a highly reactive and nitrogen-centered free radical that can induce airway inflammation, like asthma and acute bronchitis (Shima & Adachi , 2000). NO_2 is also a major precursor for a number of harmful secondary pollutants. The most important form of a secondary pollutant is ozone (O_3). Ozone is formed by photochemical reactions of sunlight on air containing hydrocarbons and nitrogen oxides. This newly formed ozone reacts with UV light again, resulting in the production of hydroxyl radicals. These hydroxyl radicals are the first step in the creation of smog components, including peroxyacyl nitrates that can be powerful eye irritants. But also neuronal deficits have been shown after O_3 exposure. Upon O_3 inhalation, Gackiere et al. showed a time- and dose-dependant neuronal activation pattern similar to that induced by systemic stress. This chronic stress is known to disrupt sleeping patterns, anxiety, depression and social isolation (Gackiere, Saliba et al. 2011).

b) Air pollution levels

Air pollution is usually concentrated in densely populated areas, especially in developing countries where environmental regulations are relatively lax or nonexistent, but also areas in the developed world can be highly polluted. In many developing countries the absence of surface-based air pollution monitors makes it difficult and sometimes impossible to get even a rough estimate of the abundance of a subcategory of airborne particles that epidemiologists suspect contributes to millions of premature deaths each year. Therefore, van Donkelaar etal. created a map (see figure 1) by blending total-column aerosol measurements with information about the vertical distribution of aerosols from a computer model (van Donkelaar et al. 2010). Figure 2 clearly shows that the areas with the highest concentration of PM2.5 are concentrated around the equator and especially in Northern Africa and the rapidly developing countries in Asia.

Figure 1 : Worldwide PM 2.5 concentration.

The picture shows the worldwide concentration of fine particles. The highest concentrations are found in the developing countries of Africa and Asia (Source: van Donkelaar, 2010).



III. Biological Considerations of Human Brain Development

A brief account of some basic principles of human brain development may help to better understand why and how prenatal or early postnatal environmental exposure to chemicals may give rise to adverse neurobehavioural alterations in infants and children postnatally. This brief overview can only be elementary; for a more detailed account the reader is referred to standard textbooks. The maturation of the central nervous system (CNS) is often described under the four headings of gross morphology, proliferation and migration of neurons and glial cells, neuronal differentiation, and myelinization. By the end of the embryonic stage (12th week of gestation) the organogenesis of the brain already shows division of the pros encephalon into two hemispheres occurs together

with a pronounced enlargement of the thalamus and an initial formation of the cerebellum. Towards the end of the 12th week of gestation, separate ventricles occur but the brain surface is still smooth. Its structuring into lobes through the formation of primary sulci (folds) occurs in the 4th month of gestation, such that the main lobes (frontal, parietal, occipital and temporal) become discernible. Among the deeper structures the main hemispheric connections, namely the corpus callosum and the commissurae anterior and posterior, also develop early. Brain damage during these early stages of CNS development gives rise to gross structural anomalies.

Following the formation of the primary sulci, secondary sulci are formed during the last three months of gestation, whereas tertiary sulci develop postnatally until the end of the 2nd year of life. It is important to note that the place of origin of neurons and glial cells is different from their final destination in the brain. Cells migrate to form, for example, the six cortical layers and the architecture of other brain structures. Besides migration, the maturation of neurons from their precursor cells, the neuroblasts, is another important developmental principle. Maturation includes enlargement of the cell body, storage of Nissl substance, formation of neurofibrils, arborization of axons and apical dendrites, and finally the increasing number of synaptic contacts between neurons. Although neuronal differentiation begins prenatally (the six cortical layers, for example, being already present around the 28th gestational week), much neuronal maturation extends into the first two postnatal years, such as the arborization of dendrites and synapse formation. Also, much of the myelinization of fibres occurs postnatally. Thus, both the prenatal and early postnatal phases of CNS development offer opportunities for chemical insult. It must finally be pointed out that many of the above-mentioned developmental processes and their timely orchestration, namely proliferation, migration, differentiation and myelinization of neurons, are partly under endocrine control. One prominent example is the hypothalamic-pituitary-thyroid (HPT) axis. Clinical observations show that severe congenital or dietary hypothyroid conditions during pregnancy or in the neonatal stage, if untreated, often result in cretinism associated with mental retardation. This is one mechanistic possibility of how chemicals interacting with endocrine systems may also interfere with brain development and associated dysfunctional neurobehavioural development postnatally (Porterfield S, 1994).

a) Brain

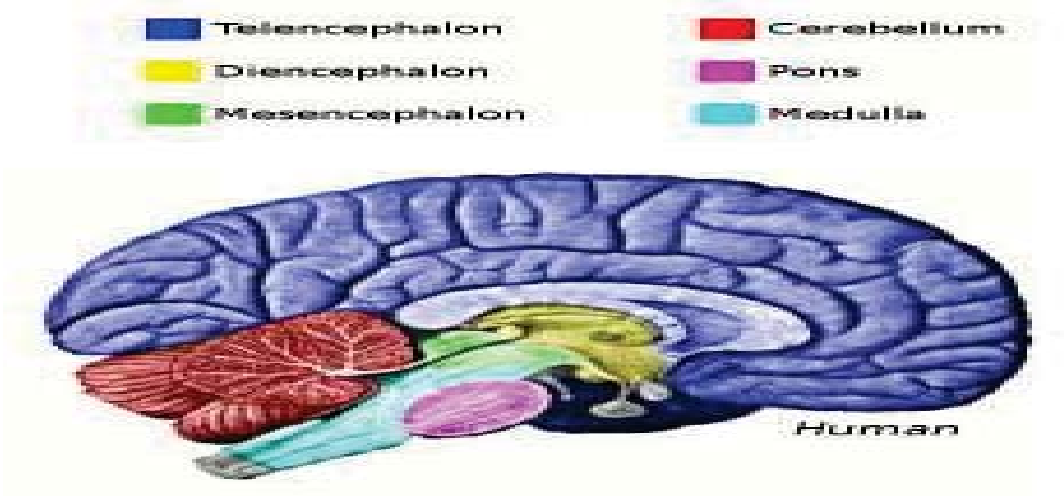
The brain, or encephalon (derived from Greek), is the centre of the nervous system. Itis the organ that is responsible for sensing, controlling and processing signals and is therefore found close to primary sensory apparatus like vision, hearing, balance, taste and smell. The brain consists of billions of neurons each connected via synapses. Neurons communicate via these synapses with chemical signals called neurotransmitters. Electrical signals are transmitted through the axons that carry action potentials to distant parts of the brain or body to target specific recipient cell. Every function will involve multiple brain regions and every brain region may be involved in several other functions. Therefore, understanding the brain is not simple and straightforward (Silverthorn, 2004).

b) Anatomy

In the early embryo, the cells that will form the nervous system are positioned in the neural plate. During the development of the embryo, neural crest cells migrate to the middle and thereby creating a neural tube. The anterior portion of the neural tube will specialize into the regions of the brain, being the forebrain, midbrain and hindbrain. The posterior part of the neural tube will form the spinal cord. Finally the six mainparts of the brain are formed: (1) the cerebrum, (2) the diencephalon, (3) the mesencephalon, (4) the cerebellum, (5) the pons and (6) the medulla oblongata (see figure 2). The cerebrum is the largest and most distinctive part of the human brain and fills most of the cranial cavity (Silverthorn, 2004).

Figure 1 : The anatomy of the human brain.

The different parts of the brain are indicated with thecolour legend. The cerebrum is by far the largest part of the brain. (Source: Ranson S.W, 1920)



c) Gray and White Matter

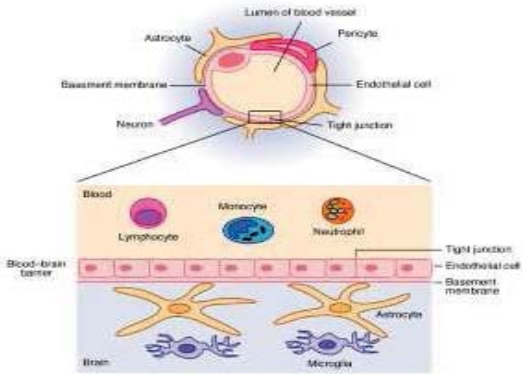
The cerebrum has distinct regions of gray and white matter. The outer layer of the cerebrum, which is only a few millimetres thick, forms the gray matter of the cerebral cortex. Gray matter consists of unmyelinated nerve cell bodies, dendrites and axon terminals. The cell bodies form layers in some parts of the brain or cluster into groups of neurons with a similar function. White matter in the cerebrum is found primarily in the interior. White matter is made up mostly of myelinated axons and contains very few cell bodies. Its pale (white) colour comes from the myelin sheaths that surround the axons. Bundles of fibres allow different regions of the cortex to communicate with each other and transfer information from one hemisphere to the other primarily through the corpus callosum (Purves et al. 2008).

d) Blood Brain Barrier

The blood brain barrier is a separation of circulation blood and the brains extracellular fluid and prevents potentially harmful particles from being delivered into the brain. It is formed by the brains capillary endothelium. These endothelial cells form tight junctions that are composed of transmembrane proteins that are anchored in the endothelial cell (see figure 3). The capillary endothelium uses selected membrane carriers and channels to move nutrients and other useful material from the blood to the brains interstitial fluid. Other transporters move wastes from the interstitial fluid into the plasma. If a water soluble molecule is not transported on one of these carriers, it cannot cross the blood brain barrier (Liddelow, 2011). Although the blood-brain barrier excludes many water-soluble substances, smaller lipid-soluble molecules can simply diffuse through the cell membranes. Because of the high demand of oxygen of the brain, oxygen can pass the blood-brain barrier freely. Neurons consume oxygen at such high rates that interruption of the blood flow to the brain can have devastating effects within only a few minutes (Pritchard, 1999).

Figure 3 : The blood brain barrier.

The blood brain barrier consists of tightly bound endothelial cells that prevent particles and immune cells from entering the brains interstitial fluid. Source: Expert Reviews in molecularmedicine@2003 Cambridge University Press.



e) Function

The brain receives sensory input from the internal and external environments. After processing these incoming signals it creates a response. However, the brain is also able to generate information and act without the external input of signals. There are three different systems that influence the output signals, being (1) the sensory system that monitors the internal and external environment and initiates reflex responses, (2) the cognitive system that is able to initiate voluntary responses and (3) a behavioural state system, which governs sleep-wake cycles and other behaviours. Cognition refers to mental processes, which include: attention, memory, Understanding a language, solving problems and making decisions. It can be natural or artificial and conscious or unconscious (Silverthorn 2004).

f) Toxicology Studies:

i. *Translocation of Particles to the Brain*

Translocation to extra pulmonary sites after respiratory tract deposition is an important mechanism for particles to cause effects in secondary organs. Whether this process occurs and to which extent, depends on several factors including particle size, solubility, site of deposition and the integrity of the epithelial lining. Elder et al. showed that ultra fine and fine particles can translocate from the lungs by penetrating pulmonary tissue and enter the capillaries, reaching other organs, including the brain by circulation (Elder, Gelein et al. 2006). As mentioned before, the blood brain barrier is supposed to inhibit harmful particles from entering the brain. However, some particles are still able to cross the blood brain barrier either because they are small enough to leak through the endothelial tight-junctions, or because they disrupt the blood brain barrier by inflammatory responses. Pollutants can also enter the brain through direct translocation. Animal studies have shown that inhaled particles can be translocated to the brain via the olfactory nerve that connects the nose and the braindirectly (Elder, Gelein et al. 2006 and Oberdorster, Sharp et al. 2004).

ii. *Neuro-inflammation and Degeneration*

The first and main form of active immune defense in the central nervous system is formed by the action of microglia. These microglia are a type of glial cells that reside in the brain and spinal cord. They respond to tissue insult with a complex array of inflammatory cytokines and actions. They are recognized as the prime components of an intrinsic brain immune system. Before neuro-inflammation became a commonly used term, scientists used the term 'reactive gliosis' (Streit, Mrak et al. 2004). This term specifically referred to the accumulation of enlarged glial cells, notably microglia and astrocytes, immediately after CNS injury had occurred. Activation of immune cells in the periphery leads to leukocyte infiltration of tissues, but this leukocyteinfiltration is absent in the brain, unless there has been destruction of the blood brain barrier. Without breakdown of the blood brain barrier, leukocytes are not able to crossthis barrier and there is a much subtler response of the brains own immune system.Although these specific responses might be included in the term neuro-inflammation, this term generally applies to a more chronic, sustained cycles of injury and response. This chronic microglia activation likely contributes to injury, loss of neurons and neuronal dysfunction (Bellucci, Westwood et al. 2004). Neuro-degeneration is the overall term for progressive loss of structures or function of neurons and axons in the central nervous system. Immune activation in the CNS is a classical feature of neuro-degeneration

iii. *IL-1 and COX-2*

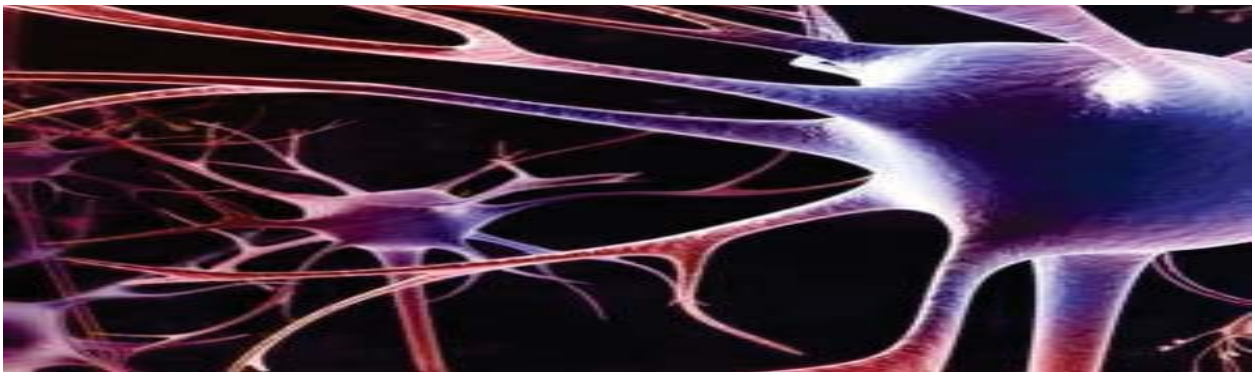
Among the pro-inflammatory molecules, cytokines are thought to play a central role inthe self-propagation of neuro-inflammation, with a prominent function for interleukin-1(IL-1). IL-1 is family of three related proteins, being Il-1a, Il-1b and Il-1ra. Normally, Il-1 is expressed at low levels, but is upregulated rapidly in response to local orperipheral insults. The specific cellular source of these proteins is unclear, butmicroglia cells appear to be the early primary source. Astrocytes and neurons havealso been reported to express Il-1. (Pearson, Rothwell et al. 1999) It remains16uncertain whether IL-1 plays a major role in the normal, healthy brain, because the expression is barely detectable. However, IL-1 has been shown to act by increasingfever, hypophagia, slow-wave sleep, sickness behaviour and neuro-endocrinechanges. It's expression is also increased in human degenerative conditions andinhibition of IL-1 in rodents reduced neuronal loss dramatically. (Rothwell & Luheshi, 2000). Cyclooxygenase (COX) generates reactive oxygen species (ROS) as a byproduct of the conversion of prostaglandin G2 to prostaglandin H2 in the synthetic pathway of prostaglandins and thromboxanes. There are two different isoforms of COX. COX-1is expressed and predominant in peripheral tissues, while COX-2 has been shown tobe expressed at high levels in the CNS and is induced by a variety of stimuli (Yamagata, Andreasson et al. 1993). It is rapidly up regulated at sites of inflammation and it is primarily expressed by neurons, whereas microglia and astrocytes are almost unlabelled. Given the fact that oxidative stress is involved in neurodegeneration,it is likely that the induction of COX-2 and the generation of freeradicals by this protein are related to the underlying mechanism (Oka & Takashima,1997).

iv. *White Matter Lesions*

White matter lesions are small area's of disrupted neurons in the white matter, commonly seen in older people, since it is a normal result of aging (Sierra, 2001). However, aging is not the only factor that induces these lesions. They also appear in the brains of people who have suffered stroke or have progressive neurological diseases and they can be induced by exposure to toxicants. While it is not clear that white matter lesions directly cause brain dysfunction, they are seen as good indicators. Namely there is a clear connection between lesions and decreases in brain volume, loss of memory and vision, and cognitive impairment (De Groot, De Leeuw et al. 2002)

iv. Cases of Air Pollution on Nervous Degeneration

a) Exposure to traffic-related air pollution and neurobehavioural functions



For this study, children from two different primary schools were selected to explore the association between traffic-related air pollution and neurobehavioral function in children (Wang, Zhang et al. 2009). The first school was located 3.5km away from primary traffic roads in the north of Quanzhou and had low traffic density. The second was located on a three-way-intersection in the centre of the city. Levels of ambient air PM10 and NO2 were measured for two days at five different school sites. The children were 8-10 years old and selected based on a questionnaire about their socioeconomic status and neurobehaviour was tested based on nine standardized tests. The NO2 levels in the polluted area where significantly higher than in the clear area. However, levels of PM10 did not show any differences. Children that were going to school in a polluted area had significantly lower scores on all nine tests, compared to the children that were going to school in de clean area. Therefore, Wang et al. state suggests that there is a significant relationship between traffic related air pollution and neurobehavioral functions in children. Similar findings were obtained by Kumar (2011) in children belonging to traffic density area of Moradabad, district of U.P. (India).

b) PAH Exposure and developmental delay

Another prospective cohort study was done by Perera et al. and evaluated the role of prenatal exposure to urban pollutants in the pathogenesis of neuro-behavioural disorders (Perera, Rauh et al. 2006). The urban pollutants included polycyclic aromatic hydrocarbons (PAHs), environmental tobacco smoke (ETS) and pesticides. The woman who participated in this cohort were Dominican or African-American, non-smokers, free of diabetes, hypertension and known HIV; did not use drugs and had resided in the area for at least one year. During the third trimester of pregnancy, personal PAH exposure was monitored for 2 consecutive days and measures of child behaviour and neurodevelopment were done with the use of the Bayley Scales of Infant Development-Revised. Infants who had been exposed to the highest concentration of PAH, scored significantly lower on the mental development index (MDI) at three years of age, compared to infants that were lower exposed. The odds of having low MDI scores were 2.89 times higher in the high exposed children, suggesting that more exposed children are potentially at risk for performance deficits.

c) Black Carbon Exposure and Cognition

The relation between black carbon and cognition among 202 Boston children was examined by Suglia et al. in a prospective birth cohort study (1989-2001) (Suglia, Gryparis et al. 2008). Pregnant woman over 18 years, receiving prenatal care at an urban community health center in Boston were fitted for enrolment. At each clinic visit during their pregnancy the women were asked about their smoking status and the smoking habits of other members of the household. Also a urine sample was taken to determine the cotinine level. The postnatal exposure of the child to second hand smoke was obtained by a questionnaire every month for the first 26 months, twice a year for the period between 26 months to 4 years and annually for the remaining years. To estimate the residential black carbon levels, data was used from pollution

measurements at more than 80 sites performed at more than 2000 different days. For the follow-up study, children were selected based on their birth weight, blood-leadlevel and ETS exposure. When the children were aged 8-11 years, cognitive tests were administered, including the Kaufman Brief Intelligence Test (K-BIT) for verbal and non verbal intelligence and the Wide Range Assessment of Memory and Learning (WRAML) for verbal and visual memory and learning (Putzke, Williams et al. 2001). In this study, long-term concentration of black carbon particles from mobile sources was associated with decreases in cognitive test scores, both on verbal and non-verbal intelligence and on memory. Socioeconomic status could have been a confounder, since it can be a determinant of cognitive abilities during childhood. Also it can determine whether a family lives close to traffic areas. However, since all families were recruited from one neighbourhood, the variability in socioeconomic status was restricted and therefore the potential of confounding was reduced. (Suglia, Gryparis et al. 2008). Another study conducted by Kumar and Sharma (2011) on the neurological effects of chronic exposure to black carbon in the children (N=150) of labor class in the Greater Noida, district of U.P. (India) also found a significant deterioration in their cognitive system and brain impairment.

V. Oxidative Stress Inflammation of Lungs and Brain Impairment

Oxidative stress, changes in autonomous function and progression of atherosclerosis have been hypothesised to be mechanisms of the neurological effect of urban air pollution in humans at any age (Peters A, Veronesi B, Caldero´n-Garciduen˜ as L, et al, 2006). Among them, inflammation secondary to oxidative stress appears to be the major suspected culprit for delay in conformation and maturation during developmental steps. Even though most of the available research about the inflammatory effects of air pollution refers to the lungs, there is evidence that the oxidative stress and inflammation induced by particles translates systemically beyond the lungs (Hirano S, Furuyama A, Koike E & Kobayashi T, 2006). For example, we found in an international longitudinal study of 1,003 adult subjects that particle count increased markers of systemic inflammation (IL-6 and fibrinogen peripheral levels) (Ru¨ ckerl R, Greven S, Ljungman P, et al. 2007). The major underlying hypothesis is that chronic respiratory tract inflammation may lead to brain inflammation by altering levels of circulating cytokines, such as TNF-a and IL-1. These cytokines have the ability to up regulate COX-2, a potent active mediator of inflammation, in capillary brain endothelium (Campbell A, 2004). Changes in brain cytokine and chemokine expression in mice have been directly linked to intranasal exposure to ultra fine carbon (Tin-Tin-Win-Shwe, Yamamoto S, Ahmed S, Kakeyama M,Kobayashi T, Fujimaki H, 2006). Carbon particles themselves generally adsorb transition metals (including antimony, barium, copper, ironand zinc) emitted from traffic exhaust and also from tyres and brake wear. These metals, which are mainly generated by traffic in the current urban atmospheres (Steiner M, Boller M, Schulz T, Pronk W, 2007), have been show no induce oxidative stress in the lung An alternative hypothetical mechanism of the neurological effect of air pollution is based on the observation that ultra fine particles containing metals translocate directly to the brain without entering the lung (Elder A, Gelein R, Silva V, et al., 2006). Changes in cognitive function in children have been shown to be associated with relatively low internal doses of lead (Lanphear BP, Hornung R, Khoury J, et al., 2005) and mercury. In addition to being linked to cognitive deficits in children, lead has been related toa diversity of behavioural problems (reading problems, school failure and delinquent behaviour), with a high social impact. In experimental studies, some metals, such as mercury and lead, inhibit neuronal differentiation, myelinisation and synaptogenesis (Johansson C, Castoldi AF, Onishchenko N, Manzo L, Vahter M, Ceccatelli S, 2007), but the specific mechanisms for lead induced intellectual deficits have not been fully elucidated.

a) Environmental Factors in Brain Development

A well-known constellation of factors related to neurodevelopment could all play a confounding role or they could explain differences in vulnerability of the dose–response relationship between air pollution and neurodevelopment (Bellinger DC, 2008). These factors must be considered and include, for example, the social environment (including parental psychological status), breast feeding, diet, maternal smoking, birth -weight and noise (Clark C, Martin R, van Kempen E, et al. 2006) along with other pollutants such as lead, mercury, DDT and indoor air pollutants (those originating from indoor sources, such as heating and cooking, or from microbial contaminants, such as endotoxins). Endotoxins are the common structural component of Gram-negative bacteria in indoor air that induced chronic inflammation in the rat brain (Lehnardt S, Massillon L, Follett P, et al., 2003). Therefore, it is important to examine diet, since it is a major source of antioxidants. Antioxidant defense mechanisms could be increased by dietary means (vitamins, omega-3 (docosahexaenoic acid) and omega-6 (arachidonic acid) fatty acids, and other micronutrients (zinc and folic acid)) to protect against air pollutants (Kelly FJ., 2004). Antioxidants in the lung are the first line of defense against oxygen free radicals. All of these antioxidants are free radical scavengers and they react rapidly to limit interaction with lung fluid lipids

and proteins (Beck-Speier I, Dayal N, Karg E, et al., 2005). The brain is particularly susceptible to free radical-mediated insult, due to its inherent biochemical and physiological characteristics, including high lipid content and energy requirements (Pajovic´ SB, Saicic´ ZS, Spasic´ MB & Petrovic´ VM., 2003). Reactive oxygen species are generated continuously in the nervous system during normal metabolism and neuronal activity (Gurgueira SA, Lawrence J, Coull B, Murthy GG & Gonza´lez-Flecha B., 2002). Similarly, genetic background may result in a differential susceptibility toward the oxidative stress pathway (Nebert DW & Vasiliou V., 2004). For example, antioxidant supplementation with vitamins C and E appears to modulate the effect of ozone in asthmatic children homozygous for the GSTM1 null allele (Romieu I, Castro-Giner F, Kunzli N & Sunyer J., 2008). Inflammatory cytokines released in the periphery (e.g. respiratory epithelia) upregulate the innate immune Toll-like receptor 2. Such activation and the subsequent events leading to neuro degeneration have recently been observed in lung lavage in mice exposed to ambient Los Angeles (CA, USA) particulate matter (Mohankumar SM, Campbell A, Block M, Veronesi B., 2008).

VI. Conclusion

To conclude, the study of chronic effects of air pollution should incorporate subtle health effects, such as functional delays in brain maturation and impairment of neurobehavioural competences, from early life exposures. The long-term consequences of these effects in the co-causation of neurodegenerative diseases have proved that our urban air is neurotoxic and deadly for our children and the chronic inflammatory process elicited within the respiratory tract upon exposure to outdoor and indoor air pollutants could serve as the trigger for a chain of events involving the brain. Hence, necessary steps have to be taken to put a check on this disastrous chain of air pollution.

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