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Neurodegenerative and neurological disorders by small inhaled particles

Harm J. Heusinkveld^{1,2,7}, Tina Wahle^{1,7}, Arezoo Campbell³, Remco H. S. Westerink⁴, Lang Trans⁵, Helinor Johnston⁶, Vicki Stone⁶, Flemming R. Cassee^{2,4,7}, Roel P.F. Schins^{1,7}

1. IUF-Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany

2. National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands

3. College of Pharmacy, Western University of Health Sciences, Pomona, CA , USA

4. Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands

5. Institute of Occupational Medicine, Edinburgh, UK

6. Heriot-Watt University, School of Life Sciences, Edinburgh, UK

7. AIR pollutants and Brain Aging research Group

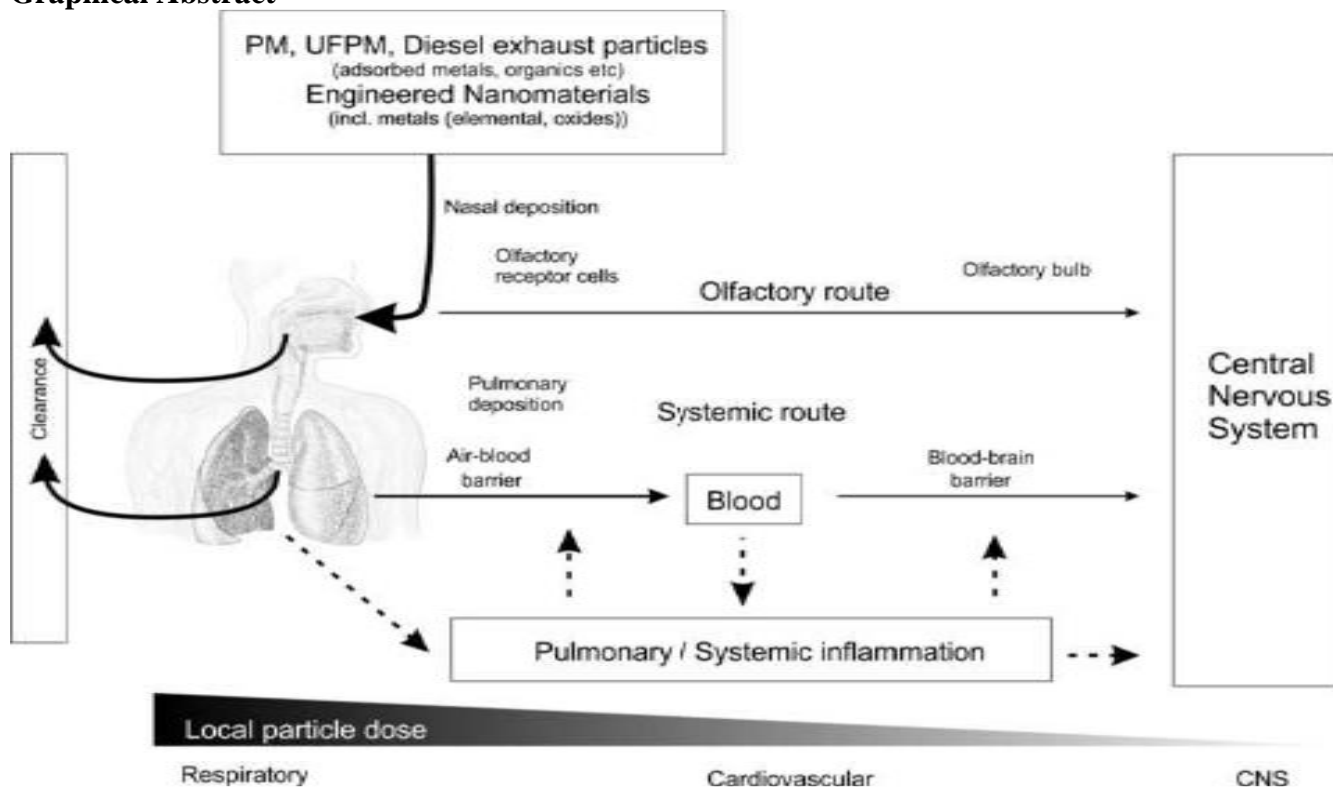
Correspondence and requests for reprints: Harm.Heusinkveld@iuf-duesseldorf.de

Abstract

The world's population is steadily ageing and as a result, health conditions related to ageing, such as dementia, have become a major public health concern. In 2001, it was estimated that there were almost 5 million Europeans suffering from Alzheimer's disease (AD) and this figure has been projected to almost double by 2040. About 40% of people over 85 suffer from AD, and another 10% from Parkinson's disease (PD). The majority of AD and PD cases are of sporadic origin and environmental factors play an important role in the aetiology. Epidemiological research identified airborne particulate matter (PM) as one of the environmental factors potentially involved in AD and PD pathogenesis. Also, cumulating evidence demonstrates that the smallest sizes of the inhalable fraction of ambient particulate matter, also referred to as ultrafine particulate matter or nano-sized particles, are capable of inducing effects beyond the respiratory system. Translocation of very small particles via the olfactory epithelium in the nose or via uptake into the circulation has been demonstrated through experimental rodent studies with engineered nanoparticles. Outdoor air pollution has been linked to several health effects including oxidative stress and neuroinflammation that may ultimately result in neurodegeneration and cognitive impairment. This review aims to evaluate the relationship between exposure to inhaled ambient particles and neurodegeneration.

Keywords: Ultrafine particles, nanomaterials, oxidative stress, neuroinflammation, Neurodegeneration

Graphical Abstract



Highlights

- Chronic exposure to inhalable PM plausibly relates to neurotoxicity and neurodegeneration
- Both direct and indirect particle effects may be implicated
- Care should be taken when extrapolating animal data to humans
- Research is needed to identify specific particle properties and underlying mechanisms

Introduction

Exposure to ambient particulate matter (PM) has been associated with lung inflammation, asthma, and fibrosis (Anderson et al., 2012) and cardiovascular disorders (Franchini and Mannucci, 2011). Observations that exposure to PM is linked with neuroinflammation indicate that the brain is among the extra-pulmonary targets of PM (for review see: (Costa et al., 2014)). During the last decade several research groups have postulated that exposure to air pollution, especially PM, could be an important environmental risk factor for neurotoxicity and more specifically may potentiate the risk of neurodevelopmental and neurodegenerative disorders (Block and Calderon-Garciduenas, 2009, Calderón-Garcidueñas et al., 2008, Calderon-Garciduenas et al., 2015, Dosunmu et al., 2007, Genc et al., 2012, Kioumourtzoglou et al., 2016, Levesque et al., 2011a, Moulton and Yang, 2012, Ranft et al., 2009, Schikowski et al., 2015).

The world's population is steadily ageing. As a result, age related diseases, such as dementia, have become a major public health concern in the first world countries (Reitz and Mayeux, 2014). In 2001, it was estimated that there were almost 5 million Europeans suffering from Alzheimer's disease (AD), and this figure is projected to almost double by the year 2040 (Ferri et al., 2005). About 40% of people over the age of 85 suffer from AD and

another 10% from Parkinson's disease (PD) (de Lau and Breteler, 2006, Ferri et al., 2005). The vast majority of AD and PD cases are sporadic in nature with no clear involvement of inheritable genetic mutations. In these cases, pesticides, metals, and ambient PM are several examples of environmental factors that have been postulated to drive disease pathogenesis (Dosunmu et al., 2007, Block and Calderon-Garciduenas, 2009, Schikowski et al.). Accumulating evidence demonstrates that in particular the smallest size-fraction of ambient PM, also referred to as ultrafine particulate matter (UFPM), is a main contributor to ambient PM-induced health effects, both locally (in the lung) and systemically (extra pulmonary sites) (Cassee et al., 2013, Delfino et al., 2005). However, the biological plausibility of the relationship between exposure to UFPM and neurodegeneration in humans remains to be elucidated. In the last decade, there has been substantial progress in this field. This paper provides a comprehensive review to assess biological plausibility of the relationship between neurological effects and exposure to inhaled ambient particles.

Exposure

When assessing the biological effects of environmental factors it is important to consider possible exposure routes and evidence for actual exposure. This is particularly important in those cases in which compounds affect multiple systems and induce a variety of effects. Inhalable ambient PM is a complex air-suspended mixture of particles varying with respect to particle number, size, surface area and chemical composition. This mixture comprises substances that are directly emitted into air (automotive exhaust, industrial emissions) or generated in chemical reactions. PM is roughly classified based on aerodynamic diameter into PM₁₀ (median particle diameter $\leq 10\mu\text{m}$), PM_{2.5} (median particle diameter $\leq 2.5\mu\text{m}$) and PM_{0.1} or UFPM (median particle diameter $\leq 0.1\mu\text{m}$) (Craig et al., 2008).

Composition of the mixture as well as physicochemical properties and (health) impacts vary widely depending on the source of the particles and the distance to the source (Steenhof et al., 2013). In general, industrial and automotive combustion-derived carbonaceous particles (e.g. diesel engine exhaust) as well as PM originating from automotive tire and brake wear comprise major sources of daily PM exposure for the general population in urban areas (Rohr and McDonald, 2016). Also overhead lines in (underground) electrical public transport systems generate particles in all size ranges with high levels of (transition) metals that contribute to the daily PM exposure (Loxham et al., 2013). Further sources include wood fires and the use of biomass fuels such as wood and coal for heating and cooking (Rohr and McDonald, 2016). For specific populations, occupational exposure may add considerably to the daily exposure to PM. This includes construction workers (e.g. mineral dust), industrial workers (e.g. metals, metal dust, and other (nano)materials) and people working in transportation (exhaust fumes, brake-wear dust)(Cassee et al., 2013). Additional sources of PM exposure for the general population include (indoor) exposure to tobacco smoke (primary and/or second and third-hand) and spray applications (e.g. deodorants) containing engineered ultrafine, or nano-sized particles (Semple and Latif, 2014, Vance et al., 2015).

Routes of exposure

A central question when considering the effect of inhaled particles on the central nervous system (CNS) is whether particles reach the brain. Upon their deposition, a large fraction of the particles will be removed via mucociliary clearance in the upper airways including the nasal compartment or through engulfment by macrophages, predominantly residing in the alveolar region. However, it is known from data on various engineered nanomaterials that a fraction of the inhaled particles depositing throughout the respiratory

tract, can translocate across epithelial barriers and along olfactory (olfactory route) and sensory neuronal pathways (including trigeminal and vagal afferents) to reach secondary organs including the brain (Kreyling, 2016, Oberdorster et al., 2009) (See Figure 1). The rate and amount of translocation are considered to depend on a number of factors including particle size and aggregation (small size favours translocation) and surface properties (e.g. charge, primary and secondary coatings with proteins, lipids and functional groups). Once in the circulation a subset of these particles may translocate across the blood brain barrier to the brain parenchyma (systemic route). Effects induced in secondary organs may be due to either a direct effect by the particles retained at these sites, by mediators induced by the particles at the portal of entry and released into the circulation, a combination of both, or via neuronal signals.

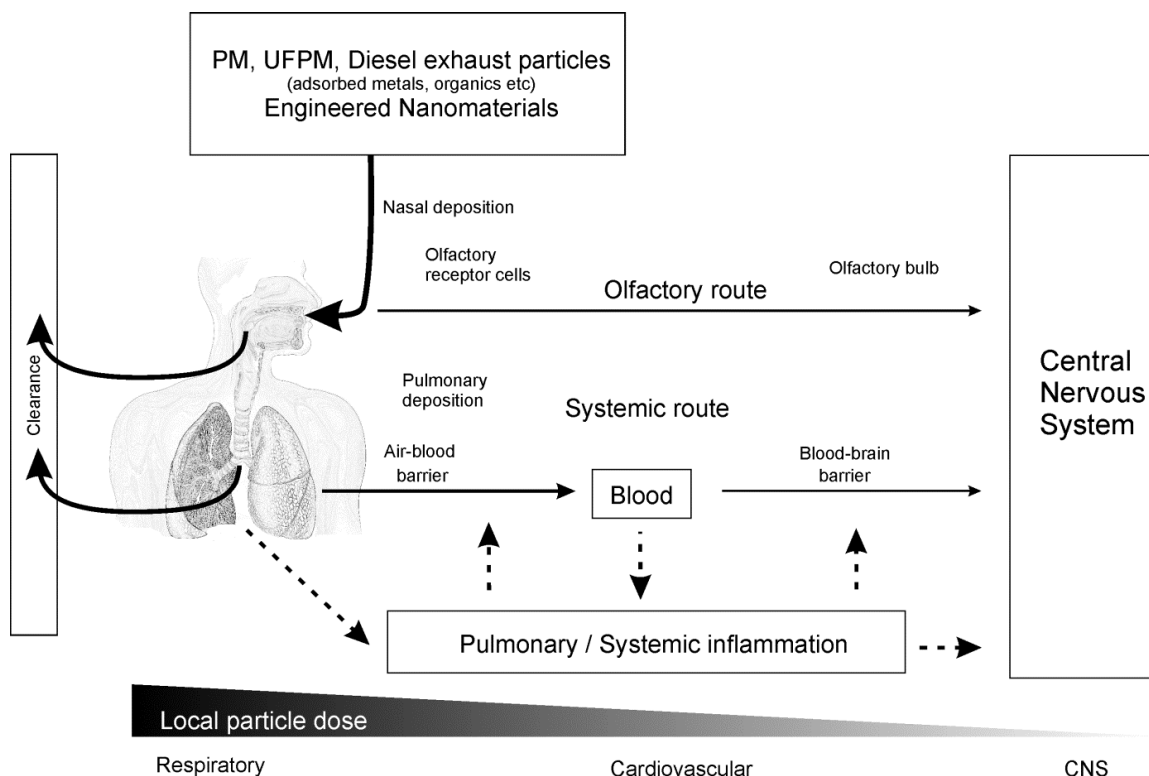


Figure 1. Principle particle translocation routes and pathways that can lead to particle accumulation the central nervous system (CNS). The preferential site of deposition in the respiratory tract is determined by particle characteristics that include size, shape and density, as well as by morphological and physiological parameters of the respiratory tract system of the exposed individual. The latter can vary considerably depending on various factors including age, physical activity, and health status. The achieved local dose and dose rate, together with the physicochemical properties of the particles and the susceptibility factors of the host, determine the extent and persistence of toxic responses at the tissue, cellular and subcellular level. Very small particles (<100 nm) have been shown to translocate to secondary organs and tissues, including the CNS via different routes (solid horizontal lines). A fraction of the particles that deposit in the nose (nasal deposition) can reach the brain via uptake over the nasal epithelium and retrograde axonal transport along the olfactory nerve. Particles that deposit in the lower respiratory tract (alveolar deposition) can translocate from the alveoli into the blood and subsequently over the blood-brain barrier into the brain. In conjunction with BBB, the term air-blood barrier (ABB) is used here, despite the obvious structural and physiological differences between both. For both routes (i.e. nose-t-brain, alveoli-blood-brain) the steep gradients of locally achievable particles

doses should be taken into account. Potential interaction between the different pathways and routes are highlighted (dashed lines).

Therefore, the possibility that UFPM physically enters the brain parenchyma or the central nervous system (direct pathway), needs to be discussed concurrent to the possibility that inhalable UFPM exerts systemic effects that may contribute to neurodegeneration (indirect pathway). The respective impact of these principally different modes of action (i.e. direct versus indirect) likely depends on exposure levels and deposition sites of the particles (size-dependent deposition pattern; Figure 2), their intrinsic reactivity (e.g. inflammogenicity) and host factors (e.g. physiology, susceptibility).

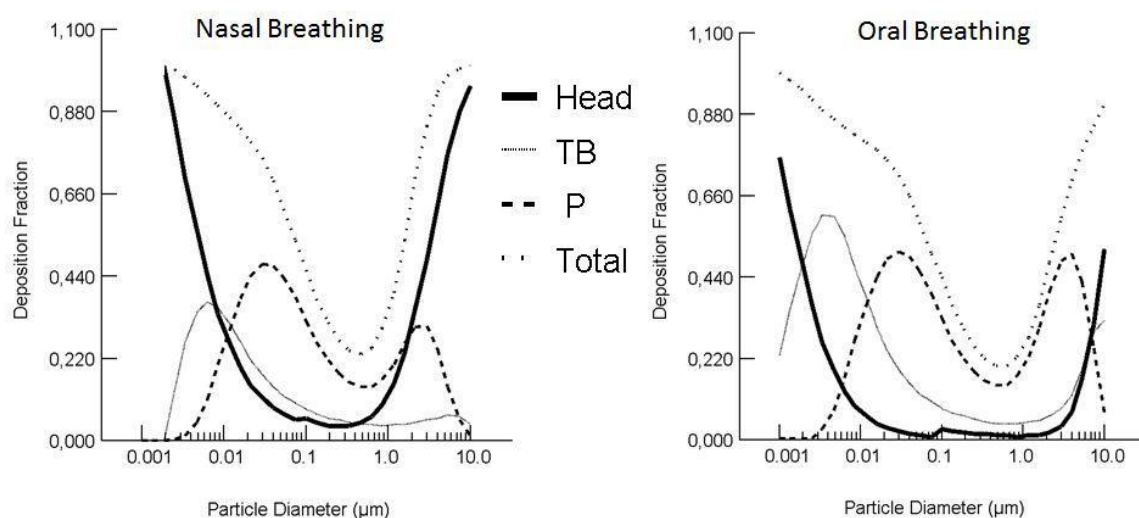


Figure 2: Modelled impact of nasal versus oral breathing on fractional particle deposition in the respiratory tract and lungs of an adult human (21 years old) based on particle size (Head: olfactory cavity plus upper respiratory tract; TB: trachio-broncheal; P: pulmonary. MPPD v3.04). Note that the probability of deposition for particles within the ultrafine range (<100nm) varies between the three regions.

The olfactory route

Uptake and retrograde axonal transport of (insoluble) particles via the olfactory nerve has been demonstrated in rodents for a number of engineered nanomaterials, including metalbased particles such as titanium dioxide, manganese oxide, colloidal gold and cadmium, but also elemental carbon (Elder et al., 2006, Wang et al., 2008, Oberdorster et al., 2004, Henriksson et al., 1999). Early research with manganese phosphate particles indicated olfactory transport of manganese in both rats and non-human primates (Dorman et al., 2002, Dorman et al., 2006). Experiments in rats using manganese oxide nanoparticles and half-sided nasal occlusion demonstrated increased levels of manganese in the corresponding contralateral olfactory bulb (Elder et al., 2006). Despite the high dose used and in view of potential bolus-artefacts occurring with nasal instillation, this inhalation study in particular provides a clear proof of the concept that uptake via the olfactory route plays a role in exposure of the CNS to particles. However, the extent to which this animal data applies to the human situation with typically long-term low-dose exposure remains to be determined. Olfactory particle deposition in humans has been compared to rats using CT-scan based 3D models of the respective nasal cavities (Garcia et al., 2015). According to the model, differences in the olfactory anatomy and physiology translate to higher nasal deposition of the smallest particles (1-7 nm) in humans compared to rats, whereas for the

larger (~100 nm) particles deposition in rats is higher, compared to humans. This study adds to earlier observations that despite the undeniable differences in physiology and anatomy of the human and rodent olfactory system, translocation of particles over the olfactory route may play a role in humans (Mistry et al., 2009, Oberdorster et al., 2004, Oberdorster et al., 2009). Investigations with iridium as well as latex nanomaterials suggest that translocation of inhaled NP could also occur along trigeminal- or vagal sensory afferents in the head and pulmonary tract (Hunter and Undem, 1999, Kreyling, 2016). However, further study is warranted to determine the contribution of these routes to the amount of uptake and potential accumulation of particles in the nervous system.

The Systemic route of Particles to the Brain: Limitations Imposed by the BBB

It has been demonstrated that a fraction of particles that deposits in the alveolar region of the lung may translocate to the systemic circulation and subsequently to extra-pulmonary organs including the brain (Elder and Oberdörster, 2006, Oberdorster et al., 2004). As an example, a rodent study using inhalation of manganese oxide nanoparticles detected increases in manganese (Mn) levels in the different brain areas (Elder et al., 2006), suggesting translocation beyond the pulmonary system and subsequent brain-wide distribution of particles upon inhalation. Extra pulmonary translocation has also been demonstrated with other engineered nanomaterials (Kreyling, 2016, Oberdorster et al., 2009).

Although the fraction of particles that translocates is small, recently developed physiologically-based pharmacokinetic (PBPK) models indicate that elimination rates are also low raising the possibility of tissue accumulation of insoluble particles following long-term exposures. This was demonstrated for both titanium dioxide nanoparticles (Bachler et al., 2015, Geraets et al., 2014) and cerium dioxide particles (Yokel et al., 2013). This clearly indicates that bio-kinetics should be considered when assessing the potential risk of particles. The blood-brain-barrier (BBB) constitutes a tight biological barrier that separates the brain from the systemic circulation. The vascular endothelium of the BBB is built and maintained by close communication with pericytes, glia and astrocytes (Alvarez et al., 2013, Campos-Bedolla et al., 2014, Banks, 2015). Compared to peripheral biological barriers, the BBB greatly reduces the possibility for inter- and transcellular leakage protecting the CNS from exposure to systemic threats such as chemicals and pathogenic agents. This also renders the brain relatively immune privileged. Several specialized transporter systems (see Figure 3) are responsible for the transport of nutrients into the brain and disposal of waste products (see (Banks, 2015) for details on the physiology of the BBB). Despite the tightness of the BBB, it has been demonstrated that blood borne particles may translocate over an intact BBB and that exposure to certain particles may increase the permeability of the BBB (Sharma et al., 2009).

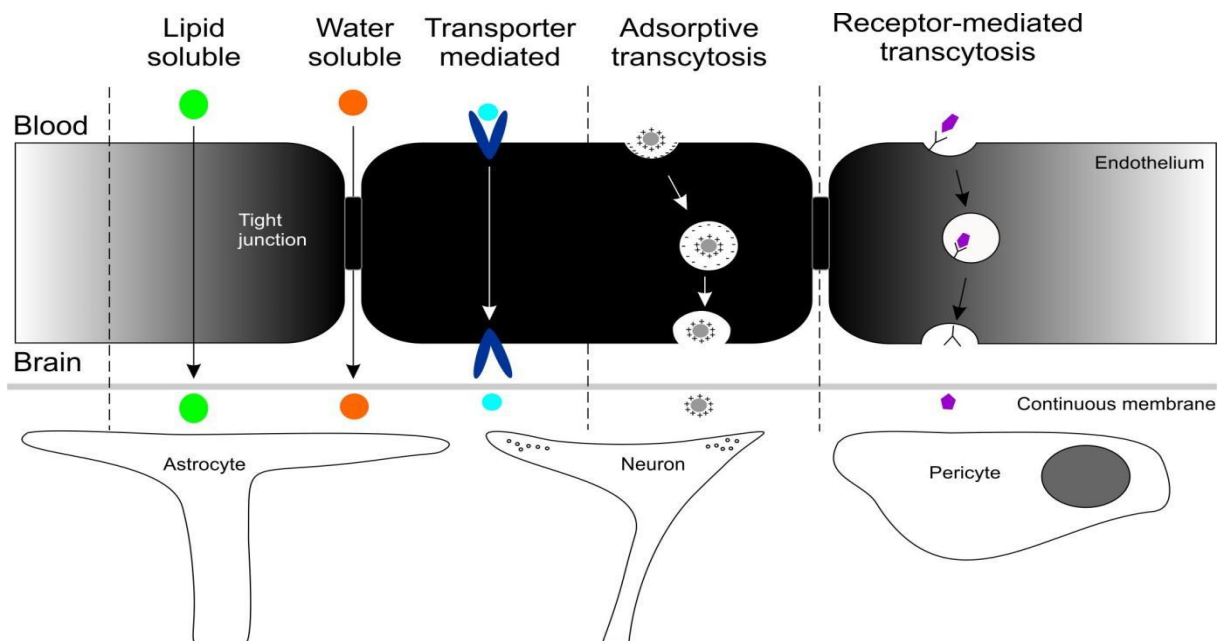


Figure 3: Schematic overview of the possible transport route of particles and/or engineered nanomaterials over the BBB.

Depending on the physicochemical properties, particles can pass an intact BBB in several ways including passive crossing by simple (passive) diffusion (lipophilic materials) or via transporter protein- or receptor-mediated, energy-dependent active transport (Mercer et al., 2013, Kafa et al., 2015) (Figure 3). One of the parameters that may determine the movement of a particle to the brain parenchyma is surface charge. The surface charge of a particle determines the formation and composition of a protein corona in biological fluids (Monopoli et al., 2011, Docter et al., 2015). Depending on the strength of particle-protein binding, particles have been demonstrated to travel across biological barriers such as the BBB and body compartments based on the type of proteins adhered to their surface (Ali et al., 2015, Dell'Orco et al., 2010). This has among others been demonstrated for particles coated with Apolipoprotein E (APOE), Polyethylene glycol (PEG) or transferrin (Kreuter et al., 2007, Kreuter et al., 2003, Yokel et al., 2013, Zensi et al., 2009, Lu et al., 2007). Much of the available knowledge originates from the field of nanomedicine, where nanosized formulations are used for targeted delivery of pharmaceuticals to the brain. However, protein-mediated transport of PM across the BBB may pose a threat to the brain as the presence of particles in the brain parenchyma may trigger activation of glial cells and may thus give rise to inflammation and oxidative stress (Sharma et al., 2009).

Apart from the protein corona that forms upon contact with biological fluids, air-borne PM may also act as a carrier for other toxic organic components such as (combustion-related) poly-aromatic hydrocarbons (PAHs) (Lim et al., 2015) metals (Schaumann et al., 2004) or microbial endotoxins (Cascio et al., 2015, Ghio et al., 2012) that may induce biological effects. An example of this is PM originating from diesel engine exhaust. It is known that this type of ambient PM consists of a solid carbonaceous nanosize core which has absorbed several components including PAHs (Omidvarborna et al., 2015). It has been hypothesized that particles therefore act as carrier for the components that cause toxicity to target organs including the brain (Mills et al., 2011).

Biological mechanisms of particle-induced neurotoxicity

Based on epidemiological, as well as *in vitro* and *in vivo* studies it is becoming

increasingly clear that inhalable PM may pose a threat to the brain. This includes the ageing brain with effects on neurodegenerative diseases such as Alzheimer's disease (Moulton and Yang, 2012, Schikowski et al., 2015), but also the developing brain (Becerra et al., 2013, Newman et al., 2013, Volk et al., 2014, Volk et al., 2013). The following section will discuss a number of different neurodegenerative diseases, the vulnerability of the developing brain and key processes or mechanisms that may link inhalable UFPM to pathological processes.

Neurodegeneration

Alzheimer's disease (AD) and Parkinson's disease (PD) represent the two most common progressive neurodegenerative diseases. Age is considered to be the major risk factor for both diseases and with the continuous rise in life expectancy the number of patients is expected to increase steeply in coming years (Thies, 2011, Kalia and Lang, 2015). Clinically, AD is characterized by a progressive loss of memory associated with cognitive deficits extending to language skills, decision-making ability, movement and recognition (Arnaiz and Almkvist, 2003, Borson and Raskind, 1997, Forstl and Kurz, 1999). In contrast, PD is characterized by a progressive loss of dopaminergic neurons in the basal ganglia (predominantly substantia nigra and striatum) primarily hampering voluntary movement (Bartels and Leenders, 2009). Although both diseases present with different primary symptoms, advanced stages of AD often display hampered movement whereas advanced stages of PD often display symptoms of dementia.

Neuropathologically, both PD and AD are characterised by the presence of protein depositions in the brain. In AD these are neurofibrillary tangles, intracellular aggregates containing hyperphosphorylated Tau proteins and senile-plaques, mainly consisting of the Amyloid- β (A β) peptide (Selkoe, 2001). In PD, proteinaceous inclusions (Lewy bodies) occur primarily in the substantia nigra area of the basal ganglia, consisting mainly of aggregated α -synuclein. Both Lewy bodies in PD and plaques and tangles in AD are associated with loss of neuronal function and degeneration of brain tissue (Bartels and Leenders, 2009, Selkoe, 2001).

Over 90% of all AD cases are of sporadic nature and the aetiology is multifactorial. Factors that reportedly play a role in disease pathogenesis include genetic predisposition and sex but also environmental factors such as air pollution, fat diet, some neurotoxic metals like lead, cadmium and arsenic, and some pesticides (Chin-Chan et al., 2015). It has been proposed that these environmental exposures play a role in the development of AD by disrupting A β homeostasis (Chin-Chan et al., 2015). Analogous to AD, the vast majority of PD cases is sporadic and of unknown (i.e. non-inheritable) origin with a suggested major role for environmental factors such as pesticide exposure and metal exposure (Elbaz and Moisan, 2008). In some epidemiological studies, inhaled UFPM has been associated with PD-related neurological effects (Guerra et al., 2013, Sriram et al., 2014). Previous epidemiological studies demonstrated an association between particulate air pollution and neurodegeneration (Calderon-Garciduenas et al., 2013, Calderon-Garciduenas et al., 2004). Moreover, epidemiological studies in Europe found an association between both AD and PD-related neurodegeneration and traffic-related air pollution exposure (Ranft et al., 2009, Oudin et al., 2016, Power et al., 2011, Ritz et al., 2016). These findings suggest that chronic exposure to traffic-related particulate matter may be involved in the pathogenesis of AD.

In addition to AD and PD, Multiple sclerosis (MS) and Amyotrophic Lateral Sclerosis (ALS) comprise neurodegenerative diseases that share underlying pathological mechanisms and link with environmental factors (Oskarsson et al., 2015, Malek et al., 2014, Trojsi et al., 2013, Ascherio, 2013). Neuropathologically, MS is characterized by neuroinflammation

gradually damaging the myelin sheaths surrounding axons leading to demyelination, scar tissue formation compromising nerve transduction and ultimately neurodegeneration (Ascherio and Munger, 2007a). Neurodegeneration in MS is a gradually worsening process and the majority of patients have remissions in between the relapses (Relapsing-Remitting form of MS). What triggers the relapse phase of MS is not well known although it has been observed that relapse rate increases during periods of high air pollution (Oikonen et al., 2003) ALS is characterised by progressive muscular paralysis throughout the body caused by selective degeneration of upper and lower motor neurons in the CNS (Ravits and La Spada, 2009). Comparable to AD and PD, ALS is characterized by intracellular protein aggregates which are thought to lead to a loss of function of intracellular organelles and ultimately cell death (Mulligan and Chakrabarty, 2013).

Impaired Neurodevelopment

In contrast to the post-mitotic adult brain, the developing brain comprises a cellular network that is still expanding and is not yet protected by a fully functional BBB. For these reasons, the developing brain is considered more sensitive to exposure to environmental toxicants. In the prenatal stage, *in utero* particle exposure via the maternal circulation and translocation over the placental barrier appears a likely scenario. In addition, the developing brain relies heavily on strict regulation of the balance between cell proliferation, migration, differentiation and cell death in order to establish new functional connections. Thus, maternal exposure to UFPM may affect fetal brain development during critical phases that may eventually predispose the progeny to neurodevelopmental disorders (Allen et al., 2014a, Allen et al., 2014b, Hougaard et al., 2015). Early life exposures may cause genetic imprinting, which may increase the risk of neurodegenerative diseases later in life (Lahiri et al., 2009). Whether particle-induced epigenetic changes during neurodevelopment may accelerate the risk of neurodegenerative diseases is an area that requires more research. Children are particularly vulnerable to the effects of air pollution for several reasons. There is higher exposure per unit of body weight as well as per unit of lung surface area. Also, brain structures are still developing and vital connections are being established during childhood. Additionally, the nervous system has a limited capacity to repair any structural damage; the destruction of brain cells or failure to establish essential connections between nerve cells, as a result of environmental insults, may therefore result in permanent and irreversible dysfunction (Sladek, 2012). In the developing brain, PM exposure may hinder neuronal network formation leading to neurodevelopmental disorders. Early studies showed that in neonatal rats, exposure to diesel exhaust changed electrophysiological responses as well as behaviour later in life (Laurie et al., 1981, Laurie and Boyes, 1981). Indeed, early-life exposure to air pollution has been linked to autism (Becerra et al., 2013, Volk et al., 2011, Volk et al., 2013, Volk et al., 2014) and an increased incidence of attention deficit/hyperactivity disorder (Newman et al., 2013). Early exposure to PM may also have more subtle effects on brain function. A prospective birth cohort study in children reported that higher exposure to ultrafine carbon black (surrogate for traffic-related particles) causes a decline in cognitive performance (Suglia et al., 2008). Animal studies recapitulate PM induced adverse CNS effects observed in epidemiological studies. Both prenatal as well as postnatal exposure can have adverse consequences. In mice, prenatal exposure to diesel exhaust particles (DEP) caused deficits in motor coordination and impulsive behaviour related to alterations in the level of monoaminergic neurotransmitters (i.e. (nor)adrenaline, dopamine and serotonin) in the brain (Yokota et al., 2013). Prenatal exposure to UFPM also impaired neuronal differentiation and caused depression-like behaviour in male mice (Davis et al., 2013). Postnatal exposure to ambient particles changed mice behaviour as assessed by preference for immediate reward (Allen et al., 2013). Duration of exposure appears to be an

important factor as reflected by the observation that a 10 month postnatal exposure to PM_{2.5} was necessary to cause impairments in spatial learning and memory as well as promotion of depressive-like behaviour in mice (Fonken et al., 2011). Male mice appear to be more sensitive to the adverse CNS changes after PM exposure as male off-springs of mouse dams, prenatally exposed to DEP and maternal stress during late gestation, were cognitively impaired (Bolton et al., 2013). Indeed, an evaluation of both male and female animals has shown that early PM exposure has more severe consequences for male mice (Allen et al., 2014a). This observation may be relevant to Autism Spectrum Disorders, which are almost 5 times more prevalent in boys compared to girls (Baio, 2014). However, the PM-induced sexdependent CNS changes are complex (Allen et al., 2014b) and require further investigation.

Mechanisms of Particle-Induced Neurotoxicity

Although neurodegenerative disorders are characterized by different phenotypes and age-of-onset, many of the proposed underlying molecular mechanisms involved are similar. This includes oxidative stress (see e.g. (Fukui and Moraes, 2008), mitochondrial dysfunction (see e.g. (Cozzolino and Carri, 2012, Dawson and Dawson, 2003) neuroinflammation/astrogliosis (see e.g. (Rodriguez and Verkhratsky, 2011), disturbance of protein homeostasis (see e.g. (Agorogiannis et al., 2004) and disturbance of intracellular calcium homeostasis (see e.g. (Gleichmann and Mattson, 2011, Mattson, 2007). At the tissue level, aggregation and accumulation of proteins are among the pathological hallmarks (see e.g. (Mulligan and Chakrabarty, 2013). Although often individual mechanisms are studied, all mechanisms mentioned here have to be considered as interconnected and are thus not mutually exclusive. In the following section cellular and molecular mechanisms are discussed by which PM, or specific constituents carried within this mixture, may influence the pathophysiology of neurodegenerative diseases.

Oxidative stress

In the brain, endogenous oxidative stress is generally high as a result of the high level of mitochondrial activity required for neuronal signalling and maintenance of ionic gradients. In specific populations of neuronal cells auto-oxidation of e.g. catecholamines also contributes to the radical burden (Smythies and Galzigna, 1998). Mitochondrial oxidative phosphorylation is the most abundant source of oxidative radicals and plays a role in normal brain ageing (Sims-Robinson et al., 2013). To cope with high levels of oxidative molecules, the brain is rich in molecules and mechanisms that neutralize radicals, including antioxidants (e.g. glutathione) and enzymatic scavengers (e.g. Cu/Zn-SOD). Chronic disturbance of the balance between the production and scavenging of oxidative radicals may result in oxidative damage to cellular components such as the intracellular organelles, proteins and mitochondrial DNA (Coppede and Migliore, 2015, Fukui and Moraes, 2008). In addition, neuronal membranes may undergo lipid peroxidation, promoting the conversion of normal molecules to potentially pathogenic constituents (Axelsen et al., 2011), leading to neuronal dysfunction via altered function of membrane-bound receptors and ion-channels (Pardillo-Díaz et al., 2015). Receptor dysfunction may subsequently lead to excitotoxicity and/or disturbances in calcium homeostasis in turn leading to cellular damage and misfolded proteins (Bezprozvanny, 2009, Garden and La Spada, 2012, Goodwin et al., 2013). Several major pathological processes in AD such as A β -induced neurotoxicity are inextricably linked to oxidative stress (see e.g. (Zhao and Zhao, 2013). In fact, oxidative stress increases the production of A β (Guglielmotto et al., 2009, Tong et al., 2005) and A β induces oxidative stress *in vivo* and *in vitro* (Mattson, 2004). Also in other neurodegenerative diseases including PD, ALS and MS, oxidative stress is thought to play an important role,

both as cause of tissue damage and as a consequence of other processes such as neuroinflammation and protein misfolding (Campbell et al., 2014, Cozzolino and Carri, 2012, Taylor et al., 2013).

Evidence from experimental studies has shown that inhalation of both PM and nanomaterials is linked to an increase in markers of oxidative stress in the lung as well as the brain (Aalapati et al., 2013, Campbell et al., 2005, Cozzolino and Carri, 2012, Elder and Oberdörster, 2006, Oppenheim et al., 2013, van Berlo et al., 2010, van Berlo et al., 2014, Veronesi et al., 2005). Thus, oxidative stress induced by inhalation of PM could initiate neurotoxicity or enhance pre-existing (e.g. A β -induced) pathology and thus form a vicious cycle that promotes the initiation and progression of neurodegenerative diseases. Although this clearly indicates that inhalation of PM may induce or enhance an oxidative stress response in the brain, it is unclear whether this is related to particles directly entering the brain (See also box 1).

Box 1 Direct and indirect effects of particles

Several studies have demonstrated oxidative stress and associated responses by PM in cell culture using CNS derived-cell lines and together with more advanced co-culture models identified potential relevant mechanisms and pathways (e.g. (Block et al., 2004, Long et al., 2007). However, such *in vitro* studies should be interpreted with caution in relation to the applied particle doses versus anticipated rates of translocation following inhalation (see also Figure 1). As an example, toxic effects of diesel exhaust particles towards dopaminergic neurons were found to be mediated by microglia-derived ROS in an phagocytosis and NADPH oxidase-dependent manner in neuro-glia cultures (Block et al., 2004). However, in an inhalation study with carbonaceous nanoparticles in p47(phox) deficient and proficient mice, an NADPH oxidase-mediated induction of oxidative stress could be identified in the lungs but not in the brains of the mice (van Berlo et al., 2014), likely as a consequence of differences in locally achieved doses for these model nanoparticles. Data on the actual amount and rate of particle translocation along and across the various routes and barriers are scarce. Studies are limited to specific (model) particles (e.g. (Kreyling, 2016, Oberdorster et al., 2004) and a generalisation should not be made because of the well-known contrasts in the physicochemical properties of particles and their impact on cellular process of uptake and transcytosis. Nevertheless, for both routes (i.e. nose-to-brain, alveoli-blood-brain) the steep gradients of locally achievable particle doses should be taken into account in the design of *in vitro* neurotoxicity studies.

Metal homeostasis

Metal ions are pivotal for the function and maintenance of nervous tissue. Physiological functions in the brain include protein stabilization, metallo-enzyme activity, and the maintenance of the myelin lining of axons (Barnham and Bush, 2014, Stephenson et al., 2014). Regulation of metal concentrations in the brain is achieved by a network of transporters in the blood-brain- and blood-cerebrospinal fluid barriers that are able to transport metals to- and from the brain parenchyma (Scheiber and Dringen, 2013, Zheng and Monnot, 2012).

Both overload and deficiency of essential metals may have serious consequences for the brain. This is illustrated by severe neurodegeneration as a result of copper overload in Menkes and Wilson's disease (Barnham and Bush, 2014, Wu et al., 2015) and accelerated brain ageing, cognitive decline and risk of epileptic seizures related to an altered brain zinc homeostasis (Hancock et al., 2014, Takeda and Tamano, 2014).

Dyshomeostasis of essential metals as well as the presence of non-essential metals are considered important factors in sporadic neurodegenerative disorders (Jomova et al., 2010, Myhre et al., 2013). Increased tissue levels of transition metals such as iron and copper have been observed concurrent with increased levels of oxidative stress and inflammatory markers in diseased brains. The close association between metals and neurodegenerative pathology is illustrated by the finding that degeneration-related protein aggregates and plaques are rich in metals such as zinc, iron and copper (Barnham and Bush, 2014, Wright and Brown, 2008). It has been observed *in vitro* that the presence of metals such as iron, aluminium and copper changes aggregation properties of α -synuclein and amyloid- β leading to formation of protein complexes (Bisaglia et al., 2009, Bolognin et al., 2013). Interestingly, many of the proteins found in aggregates (β -amyloid, Cu/Zn-SOD, α -synuclein) are involved in the regulation of the deposited metal (Barnham and Bush, 2014).

Sources responsible for PM-related environmental metal and metal-oxide exposure in the general population include automotive exhaust gases, industrial emissions, metal dust created by brake wear and the use of electrical overhead wires for public transportation. Exposure from these sources mainly consists of iron, aluminium, manganese and copper, but rare earth metals such as cerium may also be present (Loxham et al., 2015). Recently, an epidemiological study associated air pollution-related metal exposure with elevated markers of chronic systemic inflammation (Hampel et al., 2015). Furthermore, an association was observed between elevated brain concentrations of manganese, nickel and chromium in young inhabitants of Mexico-City and increased pro-inflammatory markers in different brain areas (Calderón-Garcidueñas et al., 2013). This indicates that early-life exposure to certain environmentally relevant metals may influence the development of neurodegenerative diseases later in life. Indeed, early-life exposure to lead, arsenic and cadmium in rats was recently found to associate with premature development of AD-like pathology in rats (Ashok et al., 2015). Importantly, a synergistic effect was observed following combined exposure. Although the exposure route in this study was oral instead of inhalation, this study indicates that early-life exposure to environmentally relevant metals may lead to premature brain ageing. From data on occupational exposure it is well known that manganese-containing fumes from welding processes can cause neurological and neurobehavioral symptoms comparable to PD also known as manganism (Park et al., 2014, Ordonez-Librado et al., 2008). In addition, inhalation exposure to Mn originating from industrial and vehicle exhaust emission has been associated with the risk for PD (Finkelstein and Jerrett, 2007). The latter study demonstrated that the presence of industrial Mn emissions increased the odds ratio for clinically diagnosed PD. Thus, Mn-containing traffic-related air pollution may be a contributing factor to sporadic PD. However, although the mechanistic link between high levels of exposure appears clear, the mechanistic link between long-term low-level exposures and neurodevelopmental effects and neurodegeneration are less clear (for review see: Parmalee and Aschner).

Furthermore, long-term low-level (occupational) inhalation exposure to Al dust is associated with an increased risk of AD (Bondy, 2014, Exley and Vickers, 2014). The underlying mechanism may involve Al-induced neuroinflammation (Campbell, 2006) and/or a change in tight junction proteins in the brain vasculature (Chen et al., 2008). Although the evidence provided in many studies involving human subjects is largely circumstantial, these studies indicate that air pollution-related environmental exposure to metals is associated with peripheral- as well as neuroinflammation. In this respect, it is important to realize that trans-BBB uptake as well as uptake via the olfactory mucosa and retrograde transport of metal

(containing) nanoparticles via the olfactory nerve has been observed (Elder et al., 2006, Kreyling, 2016, Kwon et al., 2013).

Protein homeostasis

A common pathological feature of many late-onset neurodegenerative diseases is the formation of intra- or extracellular protein aggregates. Diseases such as AD, PD (Agorogiannis et al., 2004) and ALS (Mulligan and Chakrabartty, 2013, Calingasan et al., 2005) exhibit different proteins associated with the pathology. For instance, in AD the extracellular plaques mainly consist of A β and the neurofibrillary tangles consist of hyperphosphorylated tau proteins. In PD, the intracellular inclusions (Lewy bodies) consist of alpha-synuclein (Bellucci et al., 2012, Breydo et al., 2012), whereas in ALS both SOD1- and A β 42 aggregates have been found (intracellularly) (Calingasan et al., 2005, Mulligan and Chakrabartty, 2013).

Protein aggregation in neurodegeneration may originate from genetic mutations in the protein processing machinery or in the gene coding for the protein. Post-translational modification such as oxidative damage to proteins may also underlie abnormal aggregation (Agorogiannis et al., 2004, Goodwin et al., 2013). Also, a disturbance in normal function of intracellular organelles, such as mitochondria and the endoplasmic reticulum (ER), as a result of calcium dyshomeostasis or glutamatergic overstimulation (excitotoxicity) may also result in production of misfolded proteins (Goodwin et al., 2013, Jiang et al., 2010, Mattson, 2012). Under physiological circumstances, damaged or misfolded proteins are cleared amongst others via autophagy. Failure of the clearance mechanism may trigger inflammatory reactions and oxidative damage.

It is unclear whether the effect of inhalable particles and in particular UFPM on protein homeostasis is direct or indirect. Although the association between metals and proteins in neurodegeneration provides a potential direct link between air pollution and neurodegeneration, it may be more likely that effects are mediated by disturbance of other processes such as oxidative damage to mitochondria or proteins, disturbance in calcium homeostasis or activation of inflammatory processes.

In view of the uptake of particles in peripheral nerves such as the vagal afferents in the pulmonary tract (see e.g. (Hunter and Undem, 1999) and the possibility of retrograde transport, it is important to realize that formation of proteinaceous plaques and aggregates in neurodegenerative diseases is not limited to the brain. In AD and ALS A β plaques are also observed in the spinal cord (Calingasan et al., 2005, Ogomori, 1989), whereas in early stages of PD protein aggregates are found in the peripheral nervous system (Braak et al., 2003). The latter led to the intriguing hypothesis that the pathological basis for parkinsonian neurodegeneration may be found in the peripheral nervous system (Clairembault et al., 2014, Grathwohl et al., 2013, Natale et al., 2008). Considering the possible implications for the origin of neurodegeneration induced by environmental factors, this hypothesis deserves more attention.

Neuroinflammation

One of the effects observed as a response to tissue damage is inflammation. Although activation of the immune system is often beneficial, prolonged inflammation can be harmful (Lucin and Wyss-Coray, 2009). Neuroinflammation is often related to a perpetuation of acute inflammatory processes and is a common observation in almost all neurodegenerative diseases (Amor et al., 2014). This is illustrated by the detection of chronically elevated levels of pro-inflammatory cytokines such as TNF- α in both brain tissue and cerebrospinal fluid of

AD and PD patients (Tarkowski et al., 2003, Taylor et al., 2013). In the case of MS, activation of the immune system via complement factors is associated with the progressive demyelination and degeneration of CNS tissue (Hundgeburth et al., 2013). However, whether the involvement of inflammation in degeneration is rather cause or consequence remains to be determined.

Exposure to (concentrated) real-life ambient PM and diesel engine exhaust has been demonstrated to exert inflammatory responses in the rodent brain (Campbell et al., 2005, Gerlofs-Nijland et al., 2010, Guerra et al., 2013, Levesque et al., 2011a, Levesque et al., 2011b, van Berlo et al., 2010). In humans, high levels of air pollution have been associated with the occurrence of neuroinflammation and markers of AD pathology. Instigation of neuroinflammation in MS triggered by periods of elevated air pollution is associated with the relapse phase of the disease (Oikonen et al., 2003, Ascherio and Munger, 2007b). Although these studies clearly indicate that air pollution is linked to induction of neuroinflammation, it is still unclear to what extent this is related to a direct action of particles entering the brain parenchyma, peripheral inflammatory effects, or a combination of both (see also Figure 1). Even though the brain is often considered immune privileged, neuroinflammatory responses secondary to peripheral inflammation are demonstrated to affect the CNS. In this respect, the observation that exposure to inhalable PM is associated with an increase in inflammatory blood markers indicative of chronic systemic inflammation is particularly important (Hampel et al., 2015). Health effects associated with this chronic inflammatory state are chronic obstructive bronchitis, pulmonary inflammation, cardiovascular system abnormalities and diabetes (Sade et al., 2015, Ibal-Mulli et al., 2002, Inoue et al., 2006, Künzli et al., 2000). It has been observed that the presence of bacterial constituents such as lipopolysaccharides (LPS) in the blood circulation leads to intracranial inflammation, which leads to progressive neurodegeneration (Qin et al., 2007). In addition, it has been demonstrated that peripheral inflammation exacerbates CNS cell loss that occurs as a result of pre-existing CNS inflammation (Hernandez-Romero et al., 2012). Mechanistically, these effects are most likely related to the presence of damage- or pathogen associated molecular pattern (DAMP/PAMP) recognizing receptors such as Toll-like receptors on the BBB epithelium or in the brain parenchyma, mediating the neuro-inflammatory response (Lucin and Wyss-Coray, 2009). The cascade of pathologic events underlying this effect involves proinflammatory cytokine-induced effects on glutamatergic neurotransmission leading to hyper-excitability and excitotoxicity contributing to neuronal loss and (synaptic) neurodegeneration (see: Vezzani and Viviani, 2015) for extensive review). Also without direct toxicity towards neuronal structures, central- and peripheral inflammation can induce changes in hippocampal synaptic plasticity (Di Filippo et al., 2013). Thus, it can be anticipated that peripheral inflammation provides an important connection between inhalable PM and the pathophysiology of neurodegenerative disorders.

Particle-Induced Disruption of the BBB

Particle exposure has been demonstrated to affect the BBB permeability. Inhalation of mixed vehicle exhaust particles in Apolipoprotein-E knock-out (ApoE^{-/-}) mice results in changes in the expression of tight-junction proteins and matrix metalloproteinase (MMP-9) activity (Oppenheim et al., 2013). By using serum from exposed mice *in vitro*, the authors demonstrated that the effect on the BBB relies on soluble factors. Although the ApoE^{-/-} mouse provides a model with an enhanced sensitivity for cardiovascular diseases, serum from exposed wild type animals produced the same effect on BBB-permeability (Oppenheim et al., 2013). In addition, exposure to engineered copper, silver and aluminium nanoparticles has

been demonstrated to exaggerate stress-induced brain effects including BBB-permeability and changes in behaviour indicative of mild cognitive impairment (Sharma and Sharma, 2007). The increase in BBB permeability upon aluminium nanoparticle exposure has been related to decreased tight junctions via changes in claudin and occludin expression in the BBB (Chen et al., 2008). Upregulation of P-glycoprotein (PgP) through activation of pathways of oxidative stress and proinflammatory cytokine production are suggested as underlying mechanisms (Dominguez et al., 2014, Rosenberg, 2014, Hartz et al., 2008). For engineered TiO₂ nanoparticles contrasting effects on the BBB homeostasis and associated translocation to the CNS have been reported (Disdier et al., 2015, Geraets et al., 2014).

Genetics & epigenetics

An increasing number of genetic mutations have been discovered that play a role in neurodegenerative disorders. Although a few genetic defects have been identified that may be considered causative, there are far more genes identified that increase susceptibility (Rohn, 2013, Lee and Cannon, 2015, Burbulla and Kruger, 2011). One of the genes that has been identified as a susceptibility gene is ApoE. Variants of the ApoE gene are linked to both cardiovascular and AD (Giau et al., 2015). Gene-environment interactions have been demonstrated by the finding that some ApoE carriers appear more affected by air pollution compared to individuals who do not have a mutation (Calderon-Garciduenas et al., 2015, Schikowski et al., 2015). The well-established role of the $\epsilon 4$ allelic variant of ApoE in cardiovascular disease, specifically on particle-induced atherogenesis also constitutes a challenging mode of action for neurodegenerative effects (See Box 2).

Box 2 Cardiovascular diseases and AD

In cardiovascular diseases, the ApoE- $\epsilon 4$ variant is associated with increased plasma levels of total cholesterol (Knouff et al., 1999), a causative factor in the development of atherosclerosis. ApoE- $\epsilon 4$ can bind efficiently to the low density lipoprotein (LDL) receptor and therefore reduce their number. This reduction will lead to a higher plasma LDL level (Knouff et al., 1999). In the CNS, ApoE- $\epsilon 4$ may play a similar role in the depletion of CNS Low density lipoprotein receptor-related protein 1 (LRP1) which contributes to the accumulation of A β -Amyloid (Kanekiyo et al., 2013). Thus, the down regulation of the Liver X Receptor (LXR) and impairment of LRP1-mediated clearance of A β -Amyloid may lead to Alzheimer like condition. As an example, accumulation of endogenous LDL nanoparticles (diameter ~ 25 nm) in atherosclerosis occurs in the arterial intimal tissue. Inside the intimal space, LDL particles are subject to oxidative modifications to produce high primarily oxidized and aggregated LDL, referred to as OxLDL (Oxidized LDL) (Catapano et al., 2000). When macrophage-mediated clearance of the OxLDL particles becomes impaired as a result of an overload of OxLDL, formation of granulomatous tissue begins (Randolph, 2008). This is the atherosclerotic plaque. The lipid burden can also generate nanosized cholesterol crystals that can grow into fibres or needles (Lim et al., 2011). In particle form, the crystals are highly inflammogenic (Grebe and Latz, 2013), whereas in fibrous form, they are able to induce frustrated phagocytosis in macrophages (Lim et al., 2011). Non-phagocytosed OxLDL particles may become blood-borne again and add to the pool of circulating OxLDL. This circulating OxLDL can subsequently be deposited on the cerebral endothelium of the BBB and thus contribute endothelial dysfunction, damage and permeability (Ang et al., 2011, Valente et al., 2014). Moreover, the OxLDL-induced inflammation is associated with a down regulation of the LXR which, in turn, down regulates the LRP1 receptor involved in the removal β -amyloid (Wildsmith et al., 2013). The relevance of this process is illustrated by detection of OxLDL antibodies in CNS fluid of Alzheimer disease patients (Kankaanpaa et al., 2009). These processes can take place over a length of time and thus constitute a

distinctive pathway for the accumulation of A β -Amyloid and development of Alzheimer disease.

In PD, leucine-rich repeat kinase 2 (LRRK2) is a gene locus that is associated with familial PD (Lesage and Brice, 2009, Lee and Cannon, 2015). However, LRRK2 mutations are considered to mediate sensitivity to environmental insults rather than be causative for PD (Lee and Cannon, 2015). In addition, mutations in the PARK2 gene, as observed in familial PD, have recently been linked to an increased mitochondrial sensitivity to copper (Aboud et al., 2015). Epigenetic changes are considered an important factor in susceptibility to environmental factors, especially in neurodevelopmental abnormalities. However, such interactions are difficult to establish because early exposure to an environmental insult may cause subtle epigenetic changes that increase susceptibility to age-related neurodegenerative disorders later in life (Modgil et al., 2014). It has for instance been demonstrated that early-life lead (Pb) exposure causes transient upregulation of APP in neonates but the levels return to normal in adulthood. However, after a prolonged lag period, APP is again upregulated in aged animals that were developmentally exposed to Pb. Interestingly, exposure of old animals (20 month old) did not cause a similar increase in APP gene expression (Basha et al., 2005, Zawia et al., 2009). Thus, it appears that an environmental insult such as Pb exposure, may cause ‘genetic imprinting’ that leads to increased vulnerability to age-related disorders. Although it is likely that exposure to PM may function as such an environmental insult, more research is warranted to draw conclusions on this matter.

Conclusion

Accumulating evidence indicates that it is plausible that (chronic) exposure to inhalable PM plays a role in the pathogenesis/pathophysiology of neurodegenerative diseases. As transport of inhalable material to the brain parenchyma has been demonstrated, direct effects on the brain are plausible. However, considering exposure levels, current paucity on particle specific translocation kinetics, and the plethora of systemic effects that are demonstrated to influence CNS pathology, it is hard to tell which route provides the strongest link. Moreover, species differences in respiratory tract morphology and physiology require careful consideration when assessing the potential effects of inhalable particles on the CNS. It is especially intriguing to consider that direct and indirect mechanisms could act together in an additive or even synergistic manner. Future experiments will need to unravel the mechanism(s) of particle-induced neurotoxicity and identify which components of inhalable PM contribute to CNS pathology.

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In view of the uptake of particles in peripheral nerves such as the vagal afferents in the pulmonary tract (see e.g. (Hunter and Udem, 1999)) and the possibility of retrograde transport, it is important to realize that formation of proteinaceous plaques and aggregates in neurodegenerative diseases is not limited to the brain. In AD and ALS A β plaques are also