The neurotoxicity of nanoparticles

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Abstract

The evidence for the neurotoxicity of nanoparticles is summarized. The sources of such particles and the ways in which they may enter the brain are listed and discussed. These include the olfactory pathway, the respiratory tract and the possibility of transport across the blood brain barrier. However, nanoparticles acting systemically can also be neurotoxic without directly entering the brain. The means by which nanoparticles can be injurious to the central nervous system include both their physical characteristics such as their form and size, and their chemical composition. Particles containing transition metals the possibility of valence flux under biological conditions, may promote pro-oxidant events in nervous tissues. Futile activation of astroglial immune responses can initiate chronic inflammatory events. The toxicity of airborne particles includes evidence of oxidative damage and heightened inflammation in the brain. The consequences of these changes may include the advancement of several prevalent neurodegenerative disorders such as Alzheimer's and Parkinson's diseases characterized by excess levels of oxidative damage and inflammatory changes. Conclusive detection of such changes in incidence consequent to particulate exposure remains elusive.

1. Introduction

Particulate materials have always been present in the atmosphere. In the past these were largely organic materials such as pollen and various plant fragments. Carbonaceous materials originating from forest fires were another intermittent component. Inorganic wind-borne dusts such as fine sand and dried ocean salt could also be found. The advent of modern industrial society has greatly expanded the number of substances found in some air samples. Airborne particulates can originate from all of the many combustion processes that prevail in contemporary society. It is well known that such particulates can be injurious to the lung and that the nature of the damage incurred is related to both the physical and the chemical nature of the inhaled materials. Thus the hazard of lung damage has increased in modern times especially in the growing urban population

The functioning of other organ systems, notably the cardiovascular system, has been shown to be affected by the inhalation of particulates. In view of the proximity of the vasculature and the alveoli of the lung, and the key role of pulmonary gas exchange, this is perhaps not surprising. However, the ability of inhaled solids to have a deleterious effect on the central nervous system is perhaps more unexpected since the mature brain has a sophisticated defensive system designed to protect it from many

agents that are present found in the circulation, that are potentially harmful to the brain.

There have been many recent reviews on the neurotoxicity of particulates and this review is focused on certain areas which have not hitherto been emphasized. The puzzle of the means by which nanoparticles, less than 100 nm in size, may have access to the brain is addressed initially. The types of damage that have been reported as a consequence of such entry are then described. This leads to the broader question of whether some types of neurological disease may owe their occurrence or progression to such particulates. Finally, it is important to understand the possible mechanisms underlying the neurotoxicity of nanoparticles. The degree of reversibility and possible treatments following exposure to nanoparticles and expression of neurotoxic signs, are also relevant.

2. Sources of nanoparticles

Nanoparticles found in urban air are largely derived from incomplete combustion of fossil fuels. These include products derived from coal, gasoline and diesel oil. Such particles, while largely carbonaceous, also contain metals. These mixtures of organic compounds together with inorganic metal oxides can be toxic in ways that cannot be predicted by study of individual components in

isolation. More specific types of ultrafine particle containing a less complex spectrum of ingredients may be encountered in industrial settings such as metal smelting and mining, in various medical, agricultural and cosmetic preparations. While all materials have the potential for causing selective damage to the target tissue, especially the lung in the case of inhaled materials; access to the brain is less ubiquitous. More recently, engineered nanomaterials are becoming common in textiles used for clothing manufacture and in façade coatings used on wall coverings (Som et al., 2011). The unintended release of nanoparticles from these materials can broaden the population range and intensity of those exposed nanoparticles.

3.0 Means of entry of nanoparticles into the brain

3.1 The olfactory pathway

The olfactory pathway as a means of delivery of large molecules and nanoparticles to the brain has been established for some time. Bodian and Howe described the transport of the poliovirus by this means as long ago as 1941. De Lorenzo (1970) showed that colloidal gold particles could move from the olfactory epithelium to the olfactory bulb. Such entry into the brain may be by way of olfactory nerve transport of deposits from the nasal olfactory mucosa (Oberdorster et al., 2004). The degree of entrapment of materials by the nasal mucosa is very dependent on particle size. After nose-only inhalation, ultra-

fine particles with a diameter of 1-3 nm, are largely retained by the nasal mucosa (Keck et al., 2000).

3.2 Other nerve pathways of the respiratory tract

Another possible mechanism is transport along the sensory trigeminal nerves into the CNS (Mistry et al., 2009, Hunter and Dey, 1998). Nanoparticles appear to be taken up various termini of the trigeminal and other sensory nerves located at several sites in the respiratory tract including the nasopharyngeal and tracheobronchial regions (Oberdorster et al., 2009). Such entry by endocytotic particle uptake and the presynaptic nerve termini followed by retrograde axoplasmic transport along neuronal tracts, can circumvent the blood brain barrier and permit nanoparticles to enter the central nervous system.

3.3 Transport through the blood brain barrier

The blood brain barrier may be traversed or circumvented by several means:

3.3.1 Receptor mediated endocytosis.

The transfer of specific molecules into the brain can take place by their binding to a surface on the inner lining of capillaries followed by transport across the capillary epithelium and endocytotic release into brain tissue. This physiological process may be hijacked by nanoparticles. The ability of nanoparticles within the vasculature, to be directly transported into the brain across the cerebral vasculature by

endocytosis, seems to depend on both their size and the nature of the external chemistry and charge of the particle. If they are coated with surfactants such as polysorbate, nanoparticles can more readily cross the blood brain barrier (Gelperina et al., 1999, Schroeder et al., 2000).

3.3.2 Phagocytosis

In general, immune cell transfer across the BBB is restricted and very limited. However, there seems to be a minor but important entry of phagocytes into the brain which then emerge as microglia (Hickey, 1991). Any elevation of generalized oxidative stress associated with excessive levels of systemic inflammation can allow an increased recruitment of monocytes into brain tissue (Drevets et al., 2008). Oxidative stress can also activate microglia to produce inflammatory cytokines (Yang et al., 2011).

3.3.3 Disruption of blood brain barrier

The normally tight junctions of the cerebral capillaries normally severely limit diffusion of blood constituents into the brain. Nonetheless, particles with diameters less than 12 nm may be able to pass directly across the blood brain barrier (Sarin et al., 2009). However, damage to the blood brain barrier can lead to a non-specific “leakiness” where exudate from the capillaries can directly access nerve tissue. Such increased membrane permeability is known to be caused by a wide range of disorders associated with inflammatory conditions. These include Alzheimer’s disease (Ryu and McLarnon,

2009), trauma (Preston et al., 2001), multiple sclerosis (Pfeiffer et al., 2011), alcoholism (Abdul Muneer et al., 2012) and reperfusion injury (Abo Ramadan et al., 2009). Nanoparticles composed of metal oxides are able to cause cerebral edema and disrupt the blood brain barrier (Sharma et al., 2010, Trickler et al., 2012).

3.3.4 Neurotoxicity in absence of entry of triggering agents into the CNS

Deranged brain metabolism secondary to generalized systemic changes

A single intra-tracheal instillation of single walled carbon nanotubes impaired the growth of brain in mice. This effect was greater than any deficit found in other organs (Park et al., 2011). Since there was extensive evidence of systemic inflammation, ~~it may~~ this effect may ~~have been consequent to was~~ have been due to generalized ~~and chronic~~ inflammation rather than to direct cerebral penetrance of these particles (which have a high aspect ratio) into the brain. It is possible for the expression of neurotoxic changes to take place following exposure to particulate matter in the absence of frank entry of material into the brain. Highly asymmetric carbon nanotubes are especially capable of provoking inflammatory responses (Jain et al., 2011, Kim et al., 2011, Murphy et al., 2012) and can induce mesothelioma as effectively as asbestos fibers (Tagaki et al., 2008). Despite the unlikelihood of their entering the brain, such materials must also be

considered to have significant neurotoxic potential. The issue of whether inhaled particulates can alter brain function without entry not the brain, by effecting systemic stress is certainly valid and has not been considered sufficiently (Valberg et al., 2008).

4. Mechanisms underlying particulate-related neurological damage

4.1 General reactions, common to many materials

A postulated common trajectory: Inflammation leading to oxidative stress leading to DNA damage and altered genomic expression (Fig.1).

4.1.1 Inflammatory and oxidant basis of damage to CNS induced by particulates

All persistent ultrafine particles have the capacity to act as an inflammatory stimulus. This is true of airborne particles such as silica and asbestos in the lung (Fubini and Hubbard, 2003) and particles finding their way into body cavity, such as talc during surgery (Edlich et al., 2001). The harmfulness of these materials seems to be related to the immune responses mounted by the body. These are ineffective as they are unable to clear these non-proteinaceous particles. This can lead to recruitment of more macrophages, leading to a growing and prolonged focus of irritation. It is not surprising then that insoluble nanoparticles within the CNS have repeatedly been reported to lead to

evidence of heightened inflammatory and oxidative activity. Such particulates include manganese (Elder el al. 2006), iron (Wang et al., 2011), silica (Choi et al., 2010) and diesel fumes (Levesque et al., 2010, Win-Shwe et al., 2011). The consequences of particulate-related chronic inflammation know to involved oxidative stress and ultimately genetic changes. Once again, the brain appears to be no exception to such sequelae (van Berlo et al., 2010). Evidence of nanoparticle-induced excess damage attributable to oxidant free radicals has been reported (Donaldson et al., 2005, Peter et al., Wang et al., 2008, Rahman et al., 2009, Levesque et al., 2010), as well as damage to DNA (Calderon-Garciduenas et al., 2003).

4.1.2 Susceptibility of dopaminergic pathways

Nervous tissue has one neurotransmitter, dopamine that is especially vulnerable to oxidative damage (Bondy and Sharman, 2007) and is a critical component of several neural pathways. Damage to this species can have significant adverse behavioral outcomes. There is evidence that these pathways are specifically susceptible to disruption by airborne particulates (Kraft and Harry, Levesque et al., 2010, Zhang et al., 2011a, Wu et al., 2011, 2013). The fostering of oxidant free radicals, would account for the unusual susceptibility of dopaminergic systems to these materials.

Behavioral change and their neurophysiological processes are the ultimate test for adverse neurotoxic events and these have both

been reported for several metal oxides in nanoparticulate form including Pb (Oszlanczi et al., 2011), (Papp et al., 2012), Ti (Wang et al., 2011), Mn (Oszlanczi et al., 2010), Al (Zhang et al., 2011a, and Zn (Han et al., 2011). Such behavioral changes are likely to involve malfunctioning dopaminergic circuitry.

4.1.3 The form and size of particles

Large surface area confers distinctive properties upon nanoparticles. Both the harmful properties and the potential beneficial applications of nanoparticles, in large part are related to their extraordinary large surface area. This permits the superficial adsorption of a variety of gaseous and liquid materials. Such absorbed chemicals can greatly affect the biological properties of particles. In addition, surfaces of nanoparticles, by attracting reactive chemicals, can act as sites of catalytic activity accelerating processes that would otherwise be negligibly slow. The large surface area of nanoparticles, which is a strong determinant of their toxicity (Lison et al., 1997), can allow for the adsorption of transition metals on their surfaces. This is able to strongly promote redox fluxes. It is noteworthy that asbestos fibers that have been soaked with deferrioxamine in order to remove any superficially bound iron, are much less toxic than the native fibers (Goodglick and Kane, 1990). Similarly the toxicity of colloidal manganese is greatly enhanced by the presence of trace amounts of iron (HaMai et al., 2001). Synthetic iron-free nanofibers are

toxicologically inert whereas “Even the smallest iron contamination imparts radical reactivity, and toxicity” (Turci et al., 2010). Free radical production on the surface of chemically inert colloids or nanoparticles is increased by two orders of magnitude by the presence of trace amounts of transition metals activity (Yang et al., 1999, Bondy and HaMai, 2004, Voinov et al., 2011). Even bimetallic nanoparticles that are homogeneous but are composed of a redox active transition metal together with a more redox inert metal, can promote oxidant events more effectively than either metal alone (Lee and Sedlack, 2008).

Activation of materials by incomplete sequestration of the surface of particles may also apply to low molecular weight organic materials found in conjunction with many airborne particulates. Both mutagenic and oxidant species have been found to be absorbed on nanoparticles derived from combusted diesel fuel (Tahara et al., 1994, Matsumoto et al., 2005). Even gold particles, which are completely chemically inert, can bind and thus activate oxidants (Sadar et al., 2009). Nanoparticles can thus consist of a relatively inert matrix with a high capacity for binding many direct oxidants and reactive chemicals on its very large surface. Such interactions may greatly enhance the toxicity of nanoparticles (Baeza-Squiban et al., 1999).

In addition to the size and shape of nanoparticles, modification of their surface hydrophilicity can also affect the extent to which they can access brain compartments (Zhang et al., 2011b). Thus the entry into

the brain of particles and the subsequent derangements that may be initiated, are both very dependent on a range of physical and chemical characteristics. When combined with the heterogeneity of many particulates suspended in gaseous media, this complicates the task of identifying the potential neurotoxic hazards to be expected.

4.2 Mechanisms specific to individual agents

While there seem to be several features common to the mechanism of neurotoxicity of all nanoparticles, the chemical nature of their constituents obviously plays a major role in their mode of action. This more specific toxicity of chemicals is likely to be closely related to the means by which they are neurotoxic when in a form other than fine particles. Thus metals capable of valence transitions under biological conditions can cause redox flux leading to generation of reactive oxygen species. Part of the neurotoxicity of particles containing iron, manganese or copper can be attributed to such free-radical-promoting processes. The extent of leaching and dissolution of metals from particle surfaces can also determine their degree of toxicity. The particulate toxicity of metals known to promote pro-oxidant conditions due to their affinity for sulfhydryl groups, such as mercury, cadmium and zinc, will persist whether the metals are present as constituents of nanoparticles or in other forms.

5 Relation to neurological disease

5.1 Nanoparticles and the promotion of age-related neurodegenerative disorders.

Pathological changes have been reported in healthy dogs chronically exposed to heavily polluted air in Mexico City (Calderon-Garciduenas et al., 2003.). These changes included evidence of inflammation, especially in the olfactory bulb and hippocampus. Excess brain levels of metal associated with oil combustion (vanadium and nickel) were found. There was also an acceleration of Alzheimer's-type pathology. The commonalties between the pathology of air pollution and that of Alzheimer's and Parkinson's diseases include early pathology in the olfactory bulb, and pathways with olfactory deficits being one of the earliest findings in both diseases. In addition, exposure to urban air pollution has been shown to cause both neuroinflammation and accumulation of $A\beta_{42}$ (component of Aβ plaques) and α-synuclein (component of Lewy Bodies), leading to the suggestion that neurolodegenerative diseases can be promoted by particulate air pollution (Block et al., 2009). While these field studies are relatively uncontrolled both as to the complex number of particulate and gaseous constituents in polluted urban air and the heterogeneous strains of dog used, they are important in that they reflect a "real world" environment to which a large population is exposed. The relevance of such an ill-defined mixture may be

furthered, as it is here that crucial synergistic events between components may take place. Diesel exhaust contains over 40 constituents know to be toxic. Some of these are particulate including several heavy metals and a variety of ill-defined carbonaceous materials, while others are gaseous such as NO, CO, ozone and uncombusted hydrocarbons (Hersterberg et al., 2006).

5.2 Combined hazards can expose vulnerability

However, it is obviously needed to enhance such reports by using more controlled laboratory experiments involving the inhalation of atmospheres where the gaseous and particulate components are well-defined. Such artificial designs can be especially revealing when particulate inhalation is combined with a separate stressor such as hyperthermia (Sharma and Sharma, 2007). The use of a genetically produced knockout mouse lacking an ApoE gene ~~which thus renders is~~ which renders it more liable to Alzheimer's-like pathological change, has revealed clear inflammatory changes ~~on animals exposed to inhaled~~ following inhalation of nanoparticles derived from ambient air (Campbell et al., 2009). The presence of disease such as diabetes (La Fuente et al., 2012), influenza (Elder et al., 2004) or hypertension (Elder et al., 2007) can be of value in eliciting particulate neurotoxicity. Such animal models illustrate that there may be sub-populations especial vulnerable to nanoparticulates.

6. Summary

The initiation of inflammatory events within the brain by exogenous ultrafine particles is based on several factors:

1. Although particulate inclusions may be chemically inert, their small size and large surface area can activate glial cells to express immune responses. Microglia and astroglia can be immunocompetent and microglia can be provoked into assuming phagocytic characteristics reminiscent of those of systemic macrophages (Zotova et al., 2011). These events can be further enhanced by infiltration of circulating macrophages into the brain.

2. The extensive aqueous-solid interface of very small particles in biological tissue, can act to partially chelate metal ions. In the case of transition metals capable of expressing more than one valence state under physiological conditions (Fe, Cu, Mn), this loose binding can form an effective platform for Fenton-like redox cycling activity. These fluxes can result in rapid catalytic generation of reactive oxygen species. In a manner parallel to the ability of asbestos to induce oxidative damage to DNA being dependent on traces of iron, the toxicity of small amounts of transition metals can powerfully synergize with that of nanoparticles.

7. Conclusion

In designing studies on the neurotoxicology of nanoparticles, two opposing forces are at play. One requires experimental conditions and the materials used to be well defined and with thorough investigation of a very limited number of variants. The other need is for the complexities of particle exposure in the real world to be recognized. A large range of possible interactions and synergistic events exist between particles and other components of the atmosphere. It is likely that the true hazards of complex mixtures such as polluted air of diesel fumes, cannot be understood by integration of results derived from findings derived from individual components. There is then a conflict between the need for more mechanistic understanding and the need to identify from a regulatory perspective, the true hazards of ill-defined yet prevalent assortments of materials.

While this issue remains a challenge, some unequivocal facts relating to nanoparticle exposure are unfolding. Nearly all age-related chronic disease involves up-regulation of inflammatory pathways. These are often related to the aging process and include cancer, cardiovascular disease, Alzheimer's disease, Parkinson's disease, arthritis, diabetes and obesity (Ahmed et al., 2009, Prasad et al., 2012). Despite this, effective immune function is depressed with aging resulting in increased susceptibility to infection and reduced responses to vaccination (Cannizzo et al., 2011). Thus immunosenescence involves depression of signal/noise activity leading to inappropriate, often

harmful reactions rather than to effective responses. The toxicity of airborne particulates often includes evidence of such heightened inflammation. This is not confined to lung but is broadly systemic (Yokota et al., 2005). A single, short-term inhalation exposure to diesel engine exhaust can trigger gene expression changes in rat brain to an extent comparable to those observed in the lung (van Berlo et al., 2010). It remains unclear whether observed effects in the CNS result from direct access of materials to the brain, or whether generalized systemic mediators cause them indirectly. The difficulty in addressing this is that, by the time particulate effects are found in nerve tissue, they are also often evoking more widespread reaction throughout the body.

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Figure legend

Fig. 1
Trajectory by which particulates may promote progression of neurodegenerative disorders