Journal of
Alzheimer's Disease & Parkinsonism

Devasena T et.al., J Alzheimers Dis Parkinsonism 2015, 5:1
DOI: 10.4172/2161-0460.1000178

Commentary Open Access

Nanotoxicity-Induced Alzheimer Disease and Parkinsonism: Not Further than Diagnosis

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Received date: Dec 12, 2014, **Accepted date:** Feb 13, 2015, **Published date: Feb** 20, 2015

Introduction

Nanoparticles are engineered or natural materials with minimum one dimension less than 100 nm. The society including research, medical, materials science, metal industry, food industry, electrical and electronic sectors could not resist the production and usage of nanoparticles owing to their unique mechanical, physical and chemical properties. Thus, nanotechnology has currently occupied the front desk in the cutting edge research and technology. As nanoparticles are unique their interaction with biological components like cells and their vital molecules are also unique when compared to the bulk counterparts. The high surface to volume ratio and the size of the nanoparticles help them gain entry into the environment and the living system including the human beings via different route of portal entry such as nasal/respiratory, dermal, oral and ocular [1-3].

Irrespective of their route of portal entry nanoparticles can gain entry into remote organs by various means such as i) translocation into the deeper alveoli in the lungs, ii) moving to the bloodstream by via the blood-air barrier [4] or iii) crossing the blood brain barrier to reach the brain [5]. There has been a great concern that very small agents and hydrophobic molecules including nanoparticles can penetrate the blood brain barrier (BBB) and reach the complicated neuronal network of the central nervous system (CNS). Most of the studies on the nanoparticles coated with polymer confirmed its uptake and accumulation in the brain with respect to their different hydrophobic nature with different types of polymeric coatings [6]. Earlier studies revealed the accumulation of poly (butylcyanoacrylate) nanoparticles coated with polysorbate 80 in the brain [7,8]. Moreover, the positively charged nanoparticles with lipid-coatings were also likely to be taken up across the blood-brain barrier in vitro [9]. Previously it is reported the CNS uptake of nanoparticles may be due to the adsorption of apolipoprotein E (ApoE) (a ligand for the transcytosis of low-density lipoprotein across the blood–brain barrier) onto the surface of the nanoparticles [10]. Another route of entry of nanoparticles into the CNS is independent of the BBB which include circumventricular organs and pathophysiologically damaged BBB induced by aging, injury or disease [11-14]. In the mature central nervous system, the circumventricular organs like choroid plexus are not protected by the BBB [11]. Discontinuity of the blood brain barrier allows entry of the small particles like drugs into the brain. Neural uptake of magnetic nanoparticles (MNP) in mice was reported earlier, may adopt this method to pass the BBB without affecting its permeability [12]. Moreover the previous studies on neurodegenerative disorders showed the elevated levels of inflammatory cytokines accompanied with aging, which in turn induce inflammation as observed in both acute and chronic neurodegenerative disorders. Therefore, it was confirmed that the exposure to submicron particles leads to both peripheral and/or CNS inflammation [13]. Moreover, it is suggested that this type neurodegenerative disorder may be due to the release of proinflammatory cytokines by microglial cells up on exposure to concentrated ambient particles as reported earlier using in vitro [14].

Therefore, there is lot of chance for the CNS degeneration and dysfunction [15]. Aging, infections and degeneration in human induce mind, motor and behavioral abnormalities in CNS that follow debilitating conditions, which includes, Alzheimer's and Parkinson's diseases (AD and PD), stroke, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS) and HIV-1-associated neurocognitive disorders (HAND). [16,17] Alzheimer's disease, the most prevalent neurodegenerative disorder is generally characterized by impairments of memory, cognition and behavior. Clinically, AD is characterized by loss of cortical, subcortical neurons and synapses [18]. Parkinson's disease is characterized by difficulty in maintaining balance, problems with ambulation, resting tremors, bradykinesia, and stiffness of the limbs and trunk. Medically, PD is defined by the loss of dopaminergic neurons within the substantia nigra pars compacta with subsequent loss of striatal dopaminergic projections. Amyotrophic lateral sclerosis, also known as Lou Gehrig's disease, a disorder of motor neurons described by muscle weakness, tripping, dropping items, abnormal fatigue of the arms and/or legs, slurred speech, muscle cramps and twitches. Neuropathologic hallmark of ALS is neuronal degeneration and atrophy, confined almost entirely to the upper and lower motor neurons [19].

In spite of the chance of entry, the manifestation of symptoms related to the effect of nanoparticles in the CNS occurs either after a large proportion of the neurons is damaged or upon almost completes loss of neuronal function. The nanoparticle exposure leads to impairments in normal neurons [20,21], microglia [22] and even aggravate the process of brain pathology was reported earlier [5]. Ion channels serve a subtle indicator of the condition and viability of the cells. Most of the neuronal properties, such as influencing action potential generation and the propagation of action potentials to synapse terminals were determined by voltage-gated sodium currents. This plays a key role remains to be determined in the transportation of amino acid neurotransmitters (e.g. aminobutyric acid (GABA)) and monoamines (i.e. dopamine (DA), norepinephrine, and serotonin). This function (local depolarization) of neurons was affected by the existence of nanoparticles. i.e. by modulation of the current reading to alterations in functionality [23]. Previous studies revealed that the nanoparticles can impair cell function and even induce certain cell death [20]. Exposure of metallic nanoparticles such as Ag in a neuro-endocrine cell line (PC-12 cells) induces neurotoxicity, characterized by the reduction in the level of DA. This may be due to the longer biological half-life of silver in the CNS compared to other organs. The

toxic effects on human neuron cells are due to the ability of nanoparticles to cross the biological membranes [24].

Inhaled nanoparticles can very well be taken up by the olfactory neurons as the olfactory system represents a unique interface between the nervous system and the external environment [25]. Intravenous, intraperitoneal, or intracerebral administration of gold, copper or aluminium nanoparticles (50-60 nm) were found to disrupt the BBB, as indicated by staining with albumin-bound Evans blue [5]. Inhalation of manganese in humans, via occupational exposure to welding fumes for example, can lead to respiratory symptoms and with chronic occupational exposure, to neurotoxicity the symptoms of which progress from preliminary psychiatric problems to Parkinson's-like disease, characterized by muscular contractions and rigidity, reduced muscle movement, and muscular tremors [25]. Hence, chronic exposure to even low concentrations of nanoparticles must be seriously considered in the context of neurodegenerative disorders like Parkinson's disease and Alzheimer's disease [15]. Recently, Win-Shwe et al. have highlighted the neurotoxicity induced by combustion-derived nanoparticles and manufactured or engineered nanoparticles in terms of neuroinflammation, oxidative stress, and altered gene in animal models and in humans [26]. Hence it becomes indispensable i) to review and comment on the influence of rapidly exposed nanoparticles on the CNS ii) to create awareness about the prevention of nanoparticle-induced neurodegenerative disorders like Parkinson's disease and Alzheimer's disease iii) to explore the possible treatment regime that could alleviate the neurotoxic effect of nanoparticles.

In the current scenario, carbon-containing nanoparticulates are the major hazard for the health and environment [27]. The leading members of this family are carbon nanotubes, and the exhaust particles liberated from diesel and the petrol engines. These nanomaterials alarmingly contribute to the air pollution to a considerable extent. Carbon nanotubes (CNT) are the most promising novel nanomaterials whose production rate and exposure rate is tremendously increasing due to their unique electrical, mechanical, and thermal properties, with potential wide applications in the electronics, computer, aerospace, and other industries. Larisa et al have reported that the single walled CNT suspensions were able to induce acute toxic effects in primary cultures from both, the central and peripheral nervous system of chicken embryos. The degree of toxicity partially depended on the agglomeration state of the tubes. Therefore, CNTs at high concentrations are likely to elicit adverse effects on glial cells and neurons which might lead to CNS degeneration [28]. Literature reports on experiments with rats and fish suggested that nano sized carbon particles are easily absorbed by olfactory neurons in the nose and subsequently translocated to the brain [29-31].

Currently, a tremendous increase in the use of petrol and diesel fuelled vehicles are more pronounced [32]. Consequently, diesel and petrol exhaust particles (DEPs and PEPs) are abundantly released into the atmosphere contributing to the urban air pollution. Both petrol and diesel fuels undergo combustion in automobile engines and give rise to Combustion Derived Nanoparticles. Majority of these particles have diameters less than 1μm and are known as ultrafine particles. Because of their small size, they impose dangerous effects on human health that include allergies, asthma, lung cancer and bronchitis which is subsequently exacerbated in the brain [33], thus increasing the risk of neurodegenerative disorders like Alzheimer's disease and Parkinson's disease. Exposure to atmospheric ultrafine particulate matter may cause inflammation and elicit neurological effects in humans. According to Calderon-Garciduenas et al. 2001 and 2003 [34,35], children living in the heavily polluted regions showed the signs of chronic inflammation of the respiratory tract, and damage to the nasal epithelium, which may exacerbate effects of pollutants by increasing access to the systemic circulation and the brain. Further, an enhancement in the expression of cyclooxygenase mRNA (Cox-mRNA), increased level of Cox-2 and amyloid β peptide were observed in the olfactory bulbs, cortex and the hippocampus of some subjects suggesting the manifestation of Alzheimer's disease [36].

On the whole, the literature reports on the direct and indirect effect of nanoparticles on brain have made the neurotoxicity and CNS degeneration an important issue to be addressed. Therefore, it is essential to understand the mechanism of neurotoxicity for further research and investigations. Oxidative stress (i.e., an imbalance in the oxidant-antioxidant status) and inflammation are the major neurotoxic mechanism elicited by nanoparticles [37-39]. Brain is easily susceptible to oxidative stress because of its high energy demand, low level of antioxidants, and high cellular content of lipids and proteins [14]. Nanoparticles interact with toll-like receptors and activate nicotinamide adenine dinucleotide phosphate oxidase cascades resulting in reactive oxygen species (ROS) generation and expression of genes related to proinflammatory cytokines, chemokines and apoptosis [37]. ROS in turn may activate nuclear factor κB (NFκB) which eventually promotes the transcription of the inflammatory genes tumor necrosis factor-α (TNF-α) and interleukin (IL)-8 leading to neuronal inflammation. Together, the oxidative stress and the inflammation may perturb neuronal hemostasis and leads to apoptosis, necrosis [40]. Neurodegeneration is the root of neurodegenerative diseases like Alzheimer's disease, transmissible spongiform encephalopathies, Parkinson's disease, and amyotrophic lateral sclerosis. Studies suggest that nanoparticles-associated CNS degeneration and the associated disease may be diagnosed using inflammatory and oxidative stress markers. In this context, we can very well insist that the nanoparticles-induced chronic inflammation and related neurodegeneration should never be neglected in the risk assessment of nanoparticles. In addition, newly developed nanoparticles may require risk assessment and standardized protocols and guidelines for control and regulation. For example, the unique properties of CNTs and graphene made as a dominant material in the field of materials science, medicine and electronics. However the translocation of the nanomaterials to brain through various paths leads to neuro damage. Translocation of MWCNTs through the olfactory sensory neurons or systemic circulation across the blood-brain barrier (BBB) induces oxidative stress and neurodegeneration. The toxicity studies of graphene in PC12 cell lines provide the information about brain related diseases and disorders. Overall, we have discussed that different types of nanoparticles with diverse size and morphology follows different route but to reach the brain and induce neurodegenerative effects resulting mainly in Alzheimer's disease or Parkinson's disease.

Many advanced and rapid diagnosis protocols are upcoming to diagnose the nanotoxicity in different organs. One step further, we would like to put forth that intensive research should be executed both in preliminary and advanced level on the formulation of a suitable pharmaceutical tool to combat the nanoparticles-induced neural inflammation, oxidative stress and CNS degeneration. This is very indispensable as the nanoparticles production and exposure cannot be avoided beyond a certain extent due to their high application to risk ratio. Natural or synthetic compounds with the dual potential i.e, capable of acting as both anti-inflammatory and antioxidant candidate

may be ideal for solving this problem. Literature survey on the anti-inflammatory and antioxidant compounds with minimal or no side effect has led us to a conclusion that polyphenolic compounds can full fill the gap. Leaders in the polyphenolic series are the Indian solid gold curcumin [41] and its synthetic analog bisdemethoxy curcumin analog (BDMCA), both of which have multiple pharmaceutical properties and negligible or no side effects. Earlier investigations from our own laboratory have disclosed the following parameters in connection with nanotized curcumin and BDMCA: i) antioxidant potential ii) anti-inflammatory potential iii) antitoxic potential and iv) anticancer potential. Therefore, we are of the opinion that the academic, research, medical and the industrial community should co-ordinately strive to work on the invention of ideal pharmaceutical tool to prevent or treat nanoparticle induced neurotoxicity which is the root cause for Alzheimer's disease and Parkinson's disease. This will drive the researchers to move further than diagnosis.

References

1. Burch WM (2002) Passage of inhaled particles into the blood circulation in humans. Circulation 106: e141-142.
2. Takenaka S, Karg E, Roth C, Schulz H, Ziesenis A, et al. (2001) Pulmonary and systemic distribution of inhaled ultrafine silver particles in rats. Environ Health Perspect 109 Suppl 4: 547-551.
3. Takeda K, Shinkai Y, Suzuki K, Yanagita S, Umezawa M, et al. (2011) [Health effects of nanomaterials on next generation]. Yakugaku Zasshi 131: 229-236.
4. Drobne D (2007) Nanotoxicology for safe and sustainable nanotechnology. Arh Hig Rada Toksikol 58: 471-478.
5. Sharma HS, Sharma A (2007) Nanoparticles aggravate heat stress induced cognitive deficits, blood-brain barrier disruption, edema formation and brain pathology. Prog Brain Res 162: 245-273.
6. Kreuter J (2001) Nanoparticulate systems for brain delivery of drugs. Adv Drug Deliv Rev 47: 65-81.
7. Calvo P, Gouritin B, Chacun H, Desmaële D, D'Angelo J, et al. (2001) Long-circulating PEGylated polycyanoacrylate nanoparticles as new drug carrier for brain delivery. Pharm Res 18: 1157-1166.
8. Gulyaev AE, Gelperina SE, Skidan IN, Antropov AS, Kivman GY, et al. (1999) Significant transport of doxorubicin into the brain with polysorbate 80-coated nanoparticles. Pharm Res 16: 1564-1569.
9. Fenart L, Casanova A, Dehouck B, Duhem C, Slupek S, et al. (1999) Evaluation of effect of charge and lipid coating on ability of 60-nm nanoparticles to cross an in vitro model of the blood-brain barrier. J Pharmacol Exp Ther 291: 1017-1022.
10. Michaelis K, Hoffmann MM, Dreis S, Herbert E, Alyautdin RN, et al. (2006) Covalent linkage of apolipoproteine to albumin nanoparticles strongly enhances drug transport into the brain. J Pharmacol Exp Ther 317: 1246-1253.
11. Spencer PS (2000). Doxorubicin and related anthracyclines. In: Spencer PS and Svhaumburg HH (eds.) Experimental and Clinical Neurotoxicology. Oxford University Press, New York pp. 529-533.
12. Kim JS, Yoon TJ, Yu KN, Kim BG, Park SJ, et al. (2006) Toxicity and tissue distribution of magnetic nanoparticles in mice. Toxicol Sci 89: 338-347.
13. Lucas SM, Rothwell NJ, Gibson RM (2006) The role of inflammation in CNS injury and disease. Br J Pharmacol 147 Suppl 1: S232-240.
14. Veronesi B, Makwana O, Pooler M, Chen LC (2005). Effects of subchronic exposures to concentrated ambient particles. VII. Degeneration of dopaminergic neurons in Apo E–/– mice. Inhal Toxicol 17: 235-241.
15. Campbell A (2004) Inflammation, neurodegenerative diseases, and environmental exposures. Ann N Y Acad Sci 1035: 117-132.
16. Minati L, Edginton T, Bruzzone MG, Giaccone G (2009) Current concepts in Alzheimer's disease: a multidisciplinary review. Am J Alzheimers Dis Other Demen 24: 95-121.
17. Nowacek A, Kosloski LM, Gendelman HE (2009) Neurodegenerative disorders and nanoformulated drug development. Nanomedicine (Lond) 4: 541-555.
18. Weimer DL, Sager MA (2009) Early identification and treatment of Alzheimer's disease: social and fiscal outcomes. Alzheimers Dement 5: 215-226.
19. Flachenecker P (2006) Epidemiology of neuroimmunological diseases. J Neurol 253 Suppl 5: V2-8.
20. Mao P, Meshul CK, Thuillier P, Goldberg NR, Reddy PH (2012) CART peptide is a potential endogenous antioxidant and preferentially localized in mitochondria. PLoS One 7: e29343.
21. Tang M, Xing T, Zeng J, Wang H, Li C, et al. (2008) Unmodified CdSe quantum dots induce elevation of cytoplasmic calcium levels and impairment of functional properties of sodium channels in rat primary cultured hippocampal neurons. Environ Health Perspect 116: 915-922.
22. Au C, Mutkus L, Dobson A, Riffle J, Lalli J, et al. (2007) Effects of nanoparticles on the adhesion and cell viability on astrocytes. Biol Trace Elem Res 120: 248-256.
23. Hussain SM, Javorina AK, Schrand AM, Duhart HM, Ali SF, et al. (2006) The interaction of manganese nanoparticles with PC-12 cells induces dopamine depletion. Toxicol Sci 92: 456-463.
24. Brooking J, Davis, SS, Illum L (2001). Transport of nanoparticles across the rat nasal mucosa. J. Drug Target 9: 267-279
25. Aschner M, Erikson KM, Dorman DC (2005) Manganese dosimetry: species differences and implications for neurotoxicity. Crit Rev Toxicol 35: 1-32.
26. Win-Shwe TT, Fujimaki H (2011) Nanoparticles and neurotoxicity. Int J Mol Sci 12: 6267-6280.
27. Buzea C, Pacheco II, Robbie K (2007) Nanomaterials and nanoparticles: sources and toxicity. Biointerphases 2: MR17-71.
28. Belyanskaya L, Weigel S, Hirsch C, Tobler U, Krug HF, et al. (2009) Effects of carbon nanotubes on primary neurons and glial cells. Neurotoxicology 30: 702-711.
29. Elder A, Gelein R, Silva V, Feikert T, Opanashuk L, et al. (2006) Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. Environ Health Perspect 114: 1172-1178.
30. Oberdorster E (2004) Manufactured nanomaterials (fullerenes, C60) induce oxidative stress in the brain of juvenile largemouth bass. Environ Health Perspect 112: 1058-1062.
31. Oberdörster G, Sharp Z, Atudorei V, Elder A, Gelein R, et al. (2004) Translocation of inhaled ultrafine particles to the brain. Inhal Toxicol 16: 437-445.
32. Karthikeyan S, Elango A, Prathima A, Raja K (2014) Environmental Effects of Nano Additive Co3O4 in Grape Seed Oil biofuel fuelled in CI Engine. Res J Chem. Environ 18: 14-18.
33. Durga M, Devasena T, Murthy PB (2013) Toxicity of exhaust nanoparticles. Afr J Pharm Pharmaco 7: 318-331.
34. Calderón-Garcidueñas L, Mora-Tiscareño A, Fordham LA, Valencia-Salazar G, Chung CJ, et al. (2003) Respiratory damage in children exposed to urban pollution. Pediatr Pulmonol 36: 148-161.
35. Calderón-Garcidueñas L, Valencia-Salazar G, Rodríguez-Alcaraz A, Gambling TM, García R, et al. (2001) Ultrastructural nasal pathology in children chronically and sequentially exposed to air pollutants. Am J Respir Cell Mol Biol 24: 132-138.
36. Peters A, Veronesi B, Calderón-Garcidueñas L, Gehr P, Chen LC, et al. (2006) Translocation and potential neurological effects of fine and ultrafine particles a critical update. Part Fibre Toxicol 3: 13.
37. Joo JY, Lee MN, Bae SO, An SSA (2013) Blood biomarkers: from nanotoxicity to neurodegeneration. SPIE Newsroom.
38. Chen G, Ke Z, Xu M, Liao M, Wang X, et al. (2012) Autophagy is a protective response to ethanol neurotoxicity. Autophagy 8: 1577-1589.

39. Bae YS, Lee JH, Choi SH, Kim S, Almazan F, et al. (2009) Macrophages generate reactive oxygen species in response to minimally oxidized low-density lipoprotein: toll-like receptor 4- and spleen tyrosine kinasedependent activation of NADPH oxidase 2. Circ Res 104: 210-218.

40. Zhang QL, Li MQ, Ji JW, Gao FP, Bai R, et al. (2011) In vivo toxicity of nano-alumina on mice neurobehavioral profiles and the potential mechanisms. Int J Immunopathol Pharmacol 24: 23S-29S.

41. Aggarwal BB, Sundaram C, Malani N, Ichikawa H (2007) Curcumin: the Indian solid gold. Adv Exp Med Biol 595: 1-75.