Exposure of Engineered Nanomaterials and Its Potential Contribution to Alzheimer’s Pathophysiology

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Being the most common form of senile dementia, Alzheimer’s disease (AD) affects 5.4 million Americans, and at least $183 billion was spent in 2011 on care of AD and other dementia patients. The problem is worsening as life expectancy continues to increase. By 2050, the projected number of AD patients could range from 11 to 16 million people in the United States alone if no cure or preventive measure for AD is found. Hence, AD has quickly become a pandemic and exacted a huge socioeconomic toll [1].

AD is manifested by a gradual onset of a progressive and irreversible cognitive decline. Memory impairment appears in the earliest stage of the disease followed by motor and sensory impairment in the later stages [2]. Genetic, biochemical, and neuropathological data indicate that AD is a multifactorial, polygenic, and complex disease. The majority of AD cases are sporadic or late onset AD (LOAD) while 5-10% of cases are early-onset familial AD (FAD) with an autosomal dominant inheritance pattern. The neuropathology of AD is characterized by the accumulation of insoluble $\alpha\beta$ amyloid peptides generated from amyloid precursor protein (APP), neurofibrillary tangles (NFTs, including apoptosis), associated neuroinflammation and cerebral redox stress in postmortem AD brain, and compromised brain energy metabolism [4,5,6]. More recent data also indicate that the BBB is leaky in AD brain [7]. However, environmental risk factors that contribute to AD pathology are not known [8].

Growing experimental evidence has implied that exposure of metal/metal oxide nanoparticles such as Fe$_2$O$_3$, CuO, and ZnO due to increasing use of these engineered nanomaterials (ENMs), may promote the pathophysiology of neurodegenerative diseases such as AD. Indeed, metal exposure has been suggested as a risk factor for AD, the most studied ones being Al, Hg, and Pb [9,10,11]. There is an abnormal enrichment of metals such as Fe, Cu, and Zn in amyloid plaques from AD brain [12,13]. Further, positive surface charges on the nanoparticles could alter the blood-brain barrier (BBB) integrity and may be a contributing factor to brain toxicity [14]. Additionally, experimental data on ovalbumin-sensitized BALB/c mice indicate that components of inhaled nanoparticulate matter may trigger a proinflammatory response in brain that could contribute to the pathophysiology of neurodegenerative diseases such as AD [15]. Moreover, nanoparticle-enhanced protein fibrilization of human $\beta2$-microglobulin has recently been shown [16], and TiO$_2$ nanoparticles has been shown to promote $\alpha\beta$ fibrillation by shortening the nucleation process [17]. Nanoparticles seem to catalyze protein fibrillation [18] which may have strong implications for many protein fibrillation and misfolding-related human diseases including AD. More importantly, epidemiological findings strongly suggest that long-term exposure to severe air pollution (highly possible exposure of metal oxide nanoparticles) is associated with the salient neuropathological features of AD: neuroinflammation, BBB disruption, and $\alpha\beta$-42 accumulation [19,20]. Moreover, our previous studies indicate that CuO nanoparticles induce potent in vitro neurotoxicity [21,22].

However, the knowledge gap exists as no relevant in vivo nanoneurotoxicity data for these metal oxide nanoparticles are currently available. In particular, in vivo CNS response to their exposure and the correlation of response to the exposure with the neuronal dysfunction in neurodegenerative diseases such as AD is not known. Hence, in vivo animal data collected from this line of warranted research may reveal in vivo mechanisms of its potential contribution to AD pathophysiology. Further, they will have broader impact upon nanoneurotoxicity and neurodegeneration research field which is currently very nascent [23]. More importantly, they will also provide some scientific basis for public policy regulation on exposure of ENMs.

References
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