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Nanoneurotoxicity and Potential Nanotheranostics for Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is the most common form of senile dementia and it is characterized by cognitive, motor and memory impairments. AD neuropathology includes toxic biomarkers, such as Aβ amyloid protein buildup between neurons disrupting connections, tau protein fibrillization and neuronal demise. These biomarkers are exacerbated with exposure to environmental borne or man-made nanoparticles or engineered nanomaterials (ENMs) as these nanoparticles are becoming more widely adopted for industrial applications. Studies suggest a link between nanoparticle exposure and neurotoxic responses, thus suggesting a contribution to AD pathology. This review summarizes research in the field of nanoparticles in terms of neurotoxic changes in the nervous system, as well as its relation to AD pathology. Studies involving silver, silica, copper oxide and iron oxide nanoparticles in mice suggest ranging neurotoxic reactions, such as disrupted neural connections, neuroinflammation, neuron cell death, redox stress, impairment of the blood-brain barrier (BBB), decrease in motor performance, demyelination of axons, decrease in long-term potentiation (LTP) and damage to DNA and brain structures. This review also examines beneficial effects of certain nanoparticles as potential therapeutic or diagnostic tools for AD.

Keywords

Alzheimer's Disease; Aβ Amyloid; Neurofibrillary Tangles; Nanoneurotoxicity; Nanotheranostics; Engineered Nanomaterials; Redox Stress; Blood-Brain Barrier; Long-Term Potentiation

Introduction

Alzheimer's disease (AD) is an irreversible brain disease resulting in decreased cognition with neurodegeneration [1]. The disease affects 5.8 million Americans, which is 10% of the population 65 and older. The problem has worsened with the baby boomer generation, as the size of the older population continues to increase. By 2050, the number of AD patients could reach 88 million if no treatment and prevention for AD are found. This devastating disease is becoming a substantial health crisis and socioeconomic burden [1].

AD is manifested by a gradual onset of a progressive and irreversible cognitive decline. The disease may begin with memory impairment, although symptoms may progressively worsen

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into sensory and motor dysfunctions [2]. AD is a disease of great complexity, as many AD cases are unexplained by family inheritance and only 5–10% of cases are early-onset due to an autosomal dominant inheritance pattern. AD may be partially attributed to Aβ amyloid protein accumulation [3], resulting in hard plaque deposits between neurons of the brain. These deposits disrupt neural connections and can cause cell death [2]. AD is also characterized by the accumulation of Aβ amyloid protein generated from amyloid precursor protein (APP) and neurofibrillary tangles (NFTs) [4] neuron cell death, together with salient neuropathological features of neuroinflammation, brain redox stress and decreased brain energy metabolism [5]. Furthermore, data indicates that the blood-brain barrier (BBB) is abnormal and leaky in AD patients [6]. Recent studies have investigated unknown environmental factors using certain tools such as high content screening-based image analysis [7], which have become important for detecting toxic responses and cell death pathways in cells [5]. Some studies have focused on the results of exposure to environmental and engineered nanoparticles and its potential link to AD pathogenesis such as maghemite (γ-Fe_2O_3) [8]. This review summarizes the literature from numerous studies that investigate the effects of different nanoparticles upon AD pathophysiology.

Nanoneurotoxicity of nanoparticles

Nanoparticles, which are simply nanometer-scale bodies of a particular material (<100 nm in diameter), are a frequent byproduct of industry. Metal oxide nanoparticles, for example, can be dispersed into the air by various metallurgical processes [9]. They can also be found in a variety of consumer products; titanium oxide nanoparticles, for example, are found in some cosmetics and skin-creams [10]. Furthermore, nanotechnology is being applied in a variety of fields. Use of ENMs is becoming more and more popular, as their small size and relatively high surface to volume ratios make them highly reactive and efficient, increasing the opportunities for nanoparticle exposure [11]. Their utilization may have been without proper caution, however. Studies performed on the effects that nanoparticles, both engineered and environmental, can have on those who are exposed to them, either through direct handling or environmental exposure, indicate that some may be detrimental to one's health. Nanoparticles primarily enter the body through the respiratory system, where they often trigger redox stress related inflammatory responses [12].

Nanoparticles also have the capacity to enter the brain. Nanoparticles that settle on the olfactory mucosa of the nasal reason are thought to move along the olfactory nerve to the olfactory bulb, where they can circulate to the brain, potentially impacting brain health and functions [8,13]. A study examining the residents of Metropolitan Mexico City, an area subject to above USEPA standard particulate matter and ozone levels, found that the pathological hallmarks marking the development of AD were found in participants far earlier than normal, with 99.5% of young individuals showing AD pathological signs in their brainstems [14]. This study shows, in a more general sense, how nanoparticulate matter can negatively impact brain health and spur the AD onset.

While nanoparticles present as a part of air-pollution appear to be detrimental to one's brain health, their exposure also results from the use and manufacture of ENMs. Metal nanoparticles, such as aluminum, mercury and lead [5,15,16] along with metal oxide

nanoparticles, such as Fe_2O_3, CuO and ZnO are among those which are frequently encountered [32–34]. Notably, an abnormal enrichment of metals in the Aβ amyloid plaques in AD brain is a common feature [18,19].

The applications of nanoparticles as drug delivery mechanisms has been explored considerably in recent years, as they allow for accurate site-specific delivery of compounds, which can limit potential side effects [20]. Indeed, nanoparticles have even been considered for the treatment of AD, as they can increase drug availability in the CNS through the enhancement of drug targeting [21]. Something that needs to be considered, however, is the potential for these particles to illicit an innate immune response. *In vitro* and *in vivo* studies testing immune responses to various nanoparticles have found a great number of them, including many metal and metal-oxide nanoparticles, exhibit pro-inflammatory effects [22]. Inflammation is a common factor in many CNS diseases, including Alzheimer's [23]. Whether a particle has a notable impact on the immune system is highly dependent on its shape and what, if anything, coats the exterior, alongside a host of other factors [20]. This variability means that not only is immune-response to nanoparticles highly variable, but in most cases particles can be engineered to avoid an undesirable immune response and, in some cases, even elicit a desirable one [24].

Nanoneurotoxicity of nanoparticles and alzheimer's disease

Silica nanoparticles (SiNPs) are among the more commonly used nanoparticles. They have been well studied about their toxic effects, such as increasing cell apoptosis and intracellular production of the reactive oxygen species (ROS) and decreasing overall cell viability [25]. In order to determine their neurotoxic effects, human SK-N-SH and mouse neuro2a (N2a) neuroblastoma cells exposed to SiNPs have been studied [25]. It was found that the cells exhibited increased amounts of both Aβ1–42 peptide and enhanced phosphorylation tau at Serine 262 and Serine 396, two AD-like hallmarks [25]. There were also an increase in the number of round cells, as well as a decrease in dendrite-like process, and a decrease in cell density [25].

Silver nanoparticles (AgNPs), which are found in many daily-use products, are also related to the development of neural disorders [26]. A study looking at levels of gene expression in mouse neurons found that the AgNPs were able to enter the mouse neuronal nuclei after 24 hours of exposure and exposure ultimately induced the deposition of Aβ amyloid in mouse N2a cells. This change came with other variations that interfere with neuron growth and differentiation [26]. Another study looking at gene expression in murine brain astrocytes, microglial and neuron cells that were exposed to the AgNPs, found an increase in the expression of inflammation related genes as well as induced APP expression which may ultimately result in an increase in Aβ amyloid protein, allowing for the formation of the Aβ amyloid plaques that are one of the AD hallmarks [27]. Additional studies examining the effects of silver, cerium oxide and cadmium telluride nanoparticles found that both silver and cerium oxide nanoparticles severely hampered the cells' Aβ uptake. All three inhibited microglia growth by arresting cell division [28].

While potential mechanisms-of-action may not have fully been explored, many metal nanoparticles, such as aluminum, mercury, lead, iron and copper are found in abnormal abundances in individuals with AD. This indicates that there is a correlation between exposure to the metal nanoparticles and the development of the disease. It is thought that the tendency for metals to increase the rate of Aβ amyloid aggregation, thereby promoting AD pathology [18,19].

Not all engineered and environmental borne nanoparticles can be directly correlated with Ad pathology. However, there are many that interfere with neural processes in such a way that they may exacerbate or enhance the disease progression. Copper oxide nanoparticles (CuONPs) are notably toxic and are known to decrease cell viability and trigger DNA fragmentation in high concentrations [29]. When human brain neuroglioma cells are subjected to CuONP exposure at a concentration of 100 μM, it causes significant amounts of cell death, indicating a dose-dependent toxic response to the nanoparticle [7].

A study observing the effects of CuONPs on hippocampal CA1 neurons suggests that they inhibit voltage-gated sodium currents, prolonging the peak rise time of the action potential and reducing the overall amplitude of the current, both of which are detrimental to neuronal functions [30]. Indeed, various studies attest to the neurotoxic effects of copper in the brain. Nanoneurotoxicity of CuONP has been investigated *in vivo* in which learning and memory was weakened [31]. CuONP neurotoxicity also suggested a slop decline in the LTP test as compared to control group rats, which, in turn, suggested an impairment of synaptic plasticity [31]. CuONPs may induce oxidative damage as well, as the levels of ROS and malonaldehyde were increased in rat brain exposed to CuONPs [31].

In vitro studies also suggest significant neurotoxic effects of CuONPs. One study compared genotoxic effects such as DNA fragmentation, DNA methylation, chromosomal damage and lipid peroxidation in addition to cytotoxic effects measured through mitochondrial reduction [29]. CuONPs may impact rat hippocampus potassium currents by blocking them upon initial exposure, which may interfere with functioning of CA1 pyramidal neurons [32]. Moreover, some studies indicate that CuONPs induce potent *in vitro* neurotoxicity [33].

Iron oxide particles are widely used in the field of biomedicine, primarily due to their magnetic properties; they are frequently used as a contrast in magnetic resonance imaging, as well as cell-tracking and other treatment purposes [34]. While they are considered to be safe in low enough quantities, some studies suggest that they have toxic effects. Studies performed on dopaminergic rat neurons exposed to iron oxide nanoparticles which have remained in the striata suggest an increase in oxidative stress, decreased neuron viability and an activation of pathways involved in apoptosis; all of these effects can lead to neurodegenerative disease [35]. Observing mice exposed to iron oxide nanoparticles over a period of 30 days found that memory and motor skills deteriorated with exposure. This was due to a variety of different effects, ranging from axon demyelination to alteration of neurotransmitter concentrations [36]. The apparent neurodegenerative effects of the iron oxide particles could indeed contribute to the AD progression as well [8].

Potential nanotheranostics for alzheimer's disease

While various nanoparticles may be neurotoxic and have the potential to exacerbate or hasten the AD development, there are some that are well studied to be fairly safe and many that are medically useful. The use of nanoparticles as drug delivery mechanisms has been mentioned previously, but nanoparticles can be useful for enabling drugs to pass through the blood-brain barrier, which poses a considerable hurdle for drug treatment of brain-based disorders [37]. In addition, administration of so-called "protective complexes" alongside nanoparticle exposure have been shown to mitigate the cytotoxicity and genotoxicity of CuONPs, one of the most well-studied and potently toxic nanoparticles [9]. Among those more benign variants are some superparamagnetic nanoparticles (Fe_3O_4) which, with the proper coatings and probes, have great potential as molecular imaging agents. In a recent study, a novel nanoparticle containing a variety of metals, dubbed MZF-PiB, was fitted with a probe designed for Aβ amyloid plaques. The nanoparticle was proven to be both nontoxic and effective in detecting Aβ amyloid plaques, making it a potential early-diagnostic tool for AD [38].

Despite the potential effects of various types of nanoparticles in exacerbating AD progression, recent research has suggested that certain sizes, shapes and types of sulfur nanoparticles (SNPs) can have the mitigating effect upon AD pathology [39]. Three kinds of brain-targeting sulfur nanoparticles (RVG@Met@SNPs) with novel morphologies: volute-like, tadpole-like and sphere-like have been designed and their different effects on Aβ aggregation, their ability to cross the BBB and their overall neurotoxicity were determined. Results suggest that smaller sized nanoparticles, such as sphere-like SNPs, may reduce Aβ peptide aggregation (61.6%) and increase cell viability (92.4%), contrary to other nanoparticles mentioned that may promote Aβ peptide aggregation and worsen AD pathology [39].

Some protein coated metal oxide/sulfide nanoparticles, such as Fe_3O_4 or CdS have also proven to be potent inhibitors of tau protein aggregation, while having no measurable toxic effects on neuroblastoma cell lines. As tau protein is the basis for NFTs that form as part of AD these particles, alongside the appropriate protein coat, are a potential avenue for AD treatment development [40]. Another potential treatment involves Fe_3O_4 superparamagnetic nanoparticles, some variations of which are proven non-toxic, that can be modified with negatively charged ions. These modified nanoparticles have been shown to decrease the rate at which Aβ amyloid-fibrils form, while remaining non-toxic; this has some potential in slowing down the progression of the disease [41]. AgNPs were found to improve spatial learning and memory in rats through the inhibition of Aβ amyloid fibril-induced neurotoxicity [42]. As a final example, cerium oxide (CeO_2) nanoparticles may be able to both reduce Aβ amyloid peptide aggregation, as well as protect against neurotoxicity in the form of oxidative damage by blocking the production of ROS and scavenging free radicals [43].

Concluding Remarks

Nanoparticles have a wide variety of consumer and industrial uses that should not be understated. Their small size and reactivity make them ideal for certain applications. They are also a somewhat inevitable byproduct of industry and an additive in a variety of consumer goods. However, largely due to their small size, nanoparticles are prone to disperse into the air, where they can be inhaled by the individual working with them or become part of air pollution that has hazardous effects upon the general population. Not only are many of these nanoparticles toxic, but many are able to enter the brain, where they contribute to or exacerbate the symptoms of neurodegenerative disorders such as AD. Given these risks, it may be wise to conduct further study on the different varieties of nanoparticles, both in current use and in development, ideally before they become too widespread. With that being said, they may also serve as starting materials for developing potential AD theranostic agents, as they can also inhibit some of the processes thought to be responsible for AD etiopathology or detect AD lesions such as Aβ amyloid plaques.

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