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Review Article

Neurotoxicity of nanoscale materials☆

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ABSTRACT

Nanotechnology has been applied in consumer products and commercial applications, showing a significant impact on almost all industries and all areas of society. Significant evidence indicates that manufactured nanomaterials and combustion-derived nanomaterials elicit toxicity in humans exposed to these nanomaterials. The interaction of the engineered nanomaterials with the nervous system has received much attention in the nanotoxicology field. In this review, the biological effects of metal, metal oxide, and carbon-based nanomaterials on the nervous system are discussed from both *in vitro* and *in vivo* studies. The translocation of the nanoparticles through the blood–brain barrier or nose to brain via the olfactory bulb route, oxidative stress, and inflammatory mechanisms of nanomaterials are also reviewed.

1. Introduction

As a rapidly growing emerging science, nanotechnology has shown a significant impact on almost all industries and all areas of society. Nanomaterials, defined by the National Nanotechnology Initiative, have at least one dimension in the range of 1–100 nm. Due to their small size, the properties of nanomaterials may differ from those of their bulk materials, showing unique chemical, physical, optical, and electrical properties. Nanotechnology involves creating and applying engineered materials at the nanoscale to take advantage of these specific properties. Humans have been exposed to many nanoparticles (NPs) originating from various activities such as combustion, welding, and biomedical applications. People working in certain industries, for example, automobile, aerospace, electronics and communications, and chemical and paint industries are at high risk of being exposed to a large amount of NPs [1–10]. As NPs persist in the environment, people living in those environments are at higher risk of NP exposure. Copper, zinc, iron, cerium, silver, gold, iron, manganese, titanium, aluminum, silica, and other carbon-based nanomaterials are some of the NPs to which humans are exposed significantly and may cause several health-related problems including neurotoxicity.

☆ The views presented in this article are those of the authors and do not necessarily reflect the views or policies of the US Food and Drug Administration.

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In recent years, a significant number of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, or Huntington's disease have been diagnosed and treated. The increased amount of environmental pollutants, including NPs, may be responsible for increasing the number of these neurodegenerative diseases. The role of the blood–brain barrier (BBB) is crucial in understanding NP toxicity in the brain. BBB separates blood from cerebrospinal fluid in the central nervous system (CNS). The BBB is an extended plasma membrane that contains tight junctions between the adjacent endothelial cells of the cerebral capillaries. The permeability properties of the BBB are of interest [1,11]. Unlike noncerebral capillaries, the cerebral endothelium does not have vesicles for macromolecular transport. Astrocytic end feet cover most (85%) of the cerebral capillary endothelial cells and they also contain a thick basement membrane [12]. The presence of such complex combinations of astrocytes, cerebral capillaries and basement membrane strongly supports the BBB function [11,13], even though establishing the clear cut roles of the basal lamina and/or astrocytic end feet in maintaining BBB permeability needs further study. When NPs reach the circulation, they may interfere with the function of the endothelial cell membrane. The effect of NPs on the cell membrane may be due to their direct toxicity, or indirectly, they may induce some cascade mechanism that disrupts the tight junctions in the BBB or alters the permeability of the membrane. It has been shown that intravenous, intraperitoneal, or intracerebral administration of Ag, Cu, or Al NPs (50–60 nm) reportedly disrupts the BBB, as indicated by staining with albumin-bound Evans blue [14]. Vesicular transport may also be stimulated by NPs in order to gain access to the CNS microenvironment to exert toxic effects in the CNS. The unique size and surface modification of NPs could deliver drugs or therapeutic agents to the brain in the development of nanomedicine. Additional research is, however, necessary in order to understand fully how NPs are translocated from the blood to the brain across the BBB.

Nanomaterials could enter the human body by different routes including inhalation, dermal penetration, ingestion, and systemic administration, by which NPs may be accumulated in different tissues and organs including the brain [15,16]. It has been indicated that the olfactory nerve pathway may serve as a portal of entry for NPs into the CNS in humans who are environmentally or occupationally exposed to airborne NPs [17–19]. De Lorenzo [18] showed that when silver-coated colloidal gold particles (50 nm) were intranasally instilled in squirrel monkeys, the NPs anterogradely moved in the axons of the olfactory nerve to the olfactory bulbs. Olfactory epithelium that has been exposed to manganese, cadmium, nickel, and cobalt nanomaterials can translocate the nanomaterials to the brain via olfactory neurons [20–25]. Therefore, full understanding of the neurotoxicity of these nanomaterials may lead to the design of safer therapeutics and reduce the side effects of these nanomaterials in future.

Having a greater surface area than their bulk counterparts, metal oxide NPs are used in various fields such as water treatment, medicine, cosmetics, and engineering, and provide superior performance in their applications. Unfortunately, almost no federal or state laws have specifically established regulations for the manufacture, transportation, use, sale, or disposal of nanomaterials [26]. For metal oxide NPs, their widespread application, small size, and large specific surface area endow them with high chemical reactivity and intrinsic toxicity, and their health effects in living creatures, especially on the nervous system, have been of concern. Metal oxide NPs are capable of translocating along the olfactory nerve pathway to the brain after intranasal instillation, and accumulating in the olfactory bulb, cortex, and cerebellum. Moreover, NP deposition in the brain can stimulate oxidative stress, inflammatory responses, and pathological changes. These observations have provided evidence that metal oxide NPs can reach the brain and cause a certain degree of tissue damage.

Metal oxide toxicity can also be induced by dissolved metal ions from the oxides. Brunner et al [27] studied the toxicity of NPs in human and rodent cell lines. They divided the tested NPs into soluble and insoluble NPs, and showed that the toxicity of soluble NPs was from the soluble metal ions released from NP dissolution prior to or after the NPs entered the neural cells. Considering the unique physicochemical properties, including small size effect, large specific surface area, and high biological surface reactivity, NPs might induce the neurotoxicological behavior and effects in organisms.

2. Neurotoxicity and mechanism of nanomaterials

2.1. *Titanium dioxide NPs*

Among several metal-based NPs, those originating from titanium have been used widely and in large quantities. Titanium dioxide (TiO_2) is the most common compound of titanium that has found a variety of uses in our lives. TiO_2 is a white, odorless, water-insoluble material that was believed to have low toxicity [28–31]. TiO_2 is a relatively stable, nonflammable material that is found naturally in the form of various ores such as rutile, anatase, and brookite. TiO_2 can also be extracted from an iron-containing mineral ($FeTiO_3$) known as ilmenite [32–36]. TiO_2 possesses certain physiochemical properties that make it useful for multiple applications. Corrosion resistance, biocompatibility, mechanical strength, whitening property, opacity, and photocatalytic, optical, and electrical activity are some of the attractive properties that have paved the way for large-scale applications of TiO_2 [37]. The National Nanotechnology Initiative of America classifies nanoparticulate TiO_2 particles as one of most widely manufactured NPs globally [38].

Industrially, 80% of TiO_2, including its nanoparticulate form (globally), is used to produce paints, varnishes, plastic, and papers. Besides these applications, nanoparticulate TiO_2 has major uses in developing various products such as cosmetics, foodstuffs, toothpaste, sun blocks, printing ink, car materials, rubber, cleaning products, materials for industrial photocatalytic applications including solar cells, and catalysts for remediation of organic matter in wastewater [39]. Toxicity of nanosized TiO_2 has yet to be completely understood despite its widespread uses. Recent toxicological studies have indicated harmful effects of TiO_2 NPs in biological systems, which is of major concern [40]. It has been recently recognized that TiO_2 may be carcinogenic to humans if inhaled [31]. As a