

Neurological toxicity of Nanomaterials in Brain: Hazard effects of these materials in Central Nervous System

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Abstract

In recent years, Nano biotechnology, bioengineering and biomedical fields finds growing interests to improve effective Nano carriers for the remedy of plentiful human illness. Nanostructured materials (NMs) are progressively applied for medical sciences that comes up as prospect medicinal carriers for the regenerative medicine, diagnosis, and drug delivery in the human biology. Because of NMs 'small size, they are competence to transverse the blood—brain barrier (BBB) and aggregate in various brain parts. NMs may cause neurotoxicity; they damage central nerves system (CNS) in vivo and induce brain diseases. Therefore, the aim is to develop safer nanocarrier system for biomedical application. Nevertheless, some studies determined that nanomaterials display a large scale of neurological toxicity impacts that cause severe cognitive impairment, neuroinflammatory disorder and increase neurodegenerative processes damage. In the aspect of neurotoxicity, nanomaterials can get to the nervous system structure and brain, these nanomaterials can access nervous tissue through the potential mechanism of neurotoxicity. Thus, primary considerations should be investigated, and researchers should deal the issues about the taxological effects of them in near future, and studies of the neurological toxicity could present a basis for the additional purpose and progress of the drug delivery system (DDS) through these nanomaterials. In this review paper, the neurological toxicity outcome of nanomaterials on the CNS and brain will be examined.

Keywords: Nano biotechnology, Nanostructured materials (NMs), Neurotoxicity, Blood–brain barrier (BBB), Drug delivery system (DDS), Central nerves system (CNS).

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1. Introduction

Nanomaterials use for different applications, for instance target-specific carriers for in vivo biosensing, diagnosis, and treatment (e.g., nanomedicine biology and medicine, drug delivery) because they have distinctive physical surface properties [1-4]. The small size of the nanomaterials can easily penetrate into cells and they can transfer across epithelial cells into blood stream to access sensitive target sites, contains the neuronal cells. Nevertheless, they trigger toxicity such as cytotoxicity, neurotoxicity and immune-toxicity due to the body distribution, change of cellular affinity and the rise of cellular uptake when they penetrate into the body. The distinctive properties of nanomaterials have also increased concerns about adverse and problematic consequences for human health or the environment. It is noteworthy that these unidentified and problematic effects can be recognized early, it can be designed products to minimize risk [5-8].

Microglia is macrophages in the CNS, and they have capability to site-directed phagocytosis. They assist to the creation of oxidative stress (OS), when they became activate. In normal condition, microglia, a phagocytic cell that induced OS, it is inactive unless encountered by potential damage and exogenous stimuli. Therefore, the production of reactive oxygen species (ROS) may be caused neurotoxicity that is mediated by some nanomaterials, caused OS and authorized by the up-regulating of mitogen activated protein (MAP) kinases to stimulate the MAP kinase signaling pathway. In that case, brain has injured due to inflammation related cytokines that are extremely conveyed in brain. Overproduction of ROS can consequently cause the loss of DNA integrity, mitochondrial dysfunction, lipid peroxidation and misfolding of proteins and finally damage neuronal cells [9]. Aging and some neurodegenerative disorder, in particular, Fatal insomnia, Parkinson and Alzheimer disease induce by neuronal damage, comprising structural defects and the loss of function that plays a critical role in these diseases. Due to, the brain and CNS are exceptionally vulnerable to oxidative stress caused by ROS because of the huge

amount of oxygen expended and oxidant production along with antioxidant deficit [10].

Nanomaterials have special physicochemical properties for instance large surface area, but they cause neurological toxicity after inserting into brain and blood-brain-barrier (BBB) that protects brain. This is the final layer (a layer of specialized endothelial cells around the brain) and the strongest biological barrier that a highly selective semipermeable border that separates the circulating blood from the brain and extracellular fluid in the CNS and protects the brain and central nervous system/spinal cord of protection in the brain [10]. The signal of brain is recorded by electrocardiogram (ECG) and data can be compressed by compressing sensing (CS) method [11, 12]. It is known to all that various nanomaterials are capable to pass blood-brain-barrier (BBB), reaching several CNS regions. With the far-reaching application of these nanomaterials, the toxicity of them have become a considerable threat to brain health and it causes potentially damaging and inducing neurotoxic effects. In terms of neurotoxicity, nanomaterials can be possibly dangerous to the CNS through numerous suitable mechanisms for example oxidative stress, autophagy, lysosome dysfunction, and the activation of evident signaling pathways. The secondary target organs, the brains, that nanomaterials can be translocated into them, they can potentially injure the CNS and can cause neurotoxic effects [13]. Specific mechanisms and pathways through which nanomaterials may utilize their effects remain essentially unidentified, hence, the possible taxological impacts of these nanomaterials on CNS function should be assessed. For the assessment of nanomaterial's neurotoxicity, purity, morphology, surface area, surface charge, coating, material solubility, and originality of the materials should be carefully considered. Therefore, for neurotoxicity, the entering nanomaterials to the nervous system (including the brain) and the potential mechanisms of neurotoxicity that nanomaterials can enter nervous tissue should be primarily considered.

1. Unintended neurotoxicity of different nanomaterials:

In recent years, many reports represent that different types of nanomaterials increase the health risk of human as exposure to them. These nanomaterials can be absorbed and discovered in many organs such as the liver, brain, kidneys, spleen, and lung. The brain is a critical organ among other organs to toxicity that caused by nanomaterials. Two important parts of the central nervous system are the brain and the spinal cord. They should be protected from injury and toxicity due to being both of them are gentle organs in human body. Different types of nanoparticles have capability to enter the Blood- Brain Barrier (BBB) in vitro and in vivo and accumulate in several brain areas. They can access nervous tissue and cause potential toxic effects on the neurological system and they convince different levels of neurotoxicity in CNS. Several studies illustrated that nanomaterials represent a broad range of neurotoxic effects that causes neuroinflammation and cognitive deficits. A varied diversity of nanomaterials was explained to enter BBB, reaching several CNS regions, containing TiO₂-NP, Ag-NP, CuO-NP, Au-NP, polymers, and etc. Although some nanomaterials cause toxicity in CNS, other materials have no toxicity for example cerium oxide (CeO₂- NP) and yttrium oxide (Y₂O₃-NP), that indicate antioxidative properties with neuroprotective effects and use as nanocarriers [5].

Extensive applications of metallic nanoparticles (NPs) rise the health hazard of human that contacts with them. An initial target of metallic NPs is the brain that consumes considerable amounts of oxygen, when they are absorbed into the body. The main mechanisms that cause the neurotoxicity of metallic NPs is Oxidative stress (OS), apoptosis, and the inflammatory response. Frequent in vivo studies have disclosed that, metallic NPs can be occupied and found in the brain, when animals were exposed to them through intravenous injection, oral administration, intranasal instillation, and intraperitoneal injection [14].

2. Some examples of nanomaterials that induce neurotoxicity

2.1. Neurotoxicological effects of silver nanoparticles (AgNPs)

There are some reports that represents neurotoxicological effects of silver nanoparticles (AgNPs) and release of ions in astrocytes, which may clarify on their risk evaluation on their potential danger to the environment and human health [15]. Indeed, some studies reported that Ag-NPs can disrupt the BBB, enhance astrocyte swelling, mitochondrial dysfunction [16] and destruction of neuron. Also, Ag-NPs can raise BBB permeability and interact with the cerebral microvascular unit, producing a perimammary cascade that reduce the viability of neuron cells, neuronal cell death and cause neurotoxicity in brain [17]. It can be mentioned that Ag-NPs represent a longer half-life within the CNS than in other organs and reside considerable time, so cause harm neurons following prolonged exposures [18]. Ag-NPs show more complex mechanisms of neurotoxicity in the brain than in other tissues. The neurotoxic effects of AgNPs and ions of silver were examined by employing rat cerebral astrocytes. Acute toxicity of silver ions was significantly more than AgNPs based on Alamar Blue assay. According to comparative studies, AgNPs raised caspase actions and cytotoxic level of exposures caused cell apoptosis by inducing intracellular ROS formation joined with JNK signal through phosphorylation. Although silver ions induced integrity of cell membrane and gave rise to cell necrosis and attaching with thiol groups of cells instantly. Non-cytotoxic level of AgNPs increased neuroinflammation via the regulation of multiple cytokine secretion from astrocytes and, demonstrating neurotoxicity of AgNPs that has particle-specific effect in AgNPs. It can be mentioned that this effect was unrelated from silver ions [15,19, 20].

2.2. Neurotoxicological effects of Aluminum (Al)

Mirshafa et al have considered the toxic effects of Aluminum (Al) on brain, also the toxicity of microparticles, nanoparticles, and Al forms ionic of an isolated mitochondria rat brain was assessed. In comparison toxicological activity of AlNPs with other types on brain represented more oxidative damage that possibly is due to additional penetration

into the brain. It can be seen growing indications about neurotoxicity of Al in humans and rodents. Also, nanoparticles of Al displayed more neurotoxicity compared to its ionic form and microparticles that probably is associated to its more penetration into the brain and more reactivity of nanoparticles [21].

2.3. Neurotoxicological effects of Mesoporous silica nanoparticles (MSNs)

Mesoporous silica nanoparticles (MSNs) is a perfect base for medicine delivery due to having distinctive structural characteristics for instance a large surface area, tunable pore size and channel, and distinct surface properties. But there are some concerns containing the negative impact of the MSNs on living cells and tissues. Ming Zhou et al investigated the biological effect of mesoporous silica nanoparticles (MSNs) on blood- brain-barrier (BBB) penetrability (across the BBB), accumulate in the brain, induce hippocampal neuronal damage, and the intervention of neurotoxicity with surface chemistry. Loss of neuron cell, nuclei shrinkage, and the collapse of neurons suggest in vivo neurotoxicity and CNS delivery of MSNs confirms a histological observation of the hippocampus and signifies neuronal damage. MSNs diminish the cell viability and induce oxidative stress with a raise of reactive oxygen species (ROS) which triggered cell death, a lessening of glutathione (GSH), lactate dehydrogenase (LDH) leakage, and the generation of malondialdehyde (MDA) in vitro assessment with the PC12 cell, a model for neuronal differentiation and dopaminergic neuron. The various MSNs induced cytotoxicity with the association of oxidative stress that correlates to the chemistry of surfaces and hence led to the neurological toxicity. The penetrability of BBB and brain accumulation of MSN were assessed with in vivo fluorescent imaging that has reported by Ming Zhou et al. It has mentioned that several minutes after injection, the concentration of the MSNs slowly reduced. Furthermore, in the peripheral tissues, for example the kidneys, liver, and spleen, the accumulation of the MSNs is similarly notable. The concentration and kinetics of accumulation in the spleen, kidneys, and liver may be greater and quicker than that in the brain according to

fluorescence intensity in these tissues. Nonetheless, there is need to more wide- ranging studies to confirm the release kinetics and permeability of the MSNs that enter the BBB and disclose the mechanism of entering of the MSNs into the brain. Also, addressing internalization mechanism and oxidative stress caused by the MSNs to disclose the base of the neurotoxicity is essential [10, 22].

2.4. Neurotoxicological effects of Titanium dioxide nanoparticles (TNPs)

Titanium dioxide nanoparticles (TNPs) is broadly utilized in several areas that impacts our day- to-day life. Hence, there is need more consideration associated with the influence of nano-TiO on human health and the ecosystem. Oxidative stress implies interaction between nano-TiO particles and living organisms that is a principal mechanism among several mechanisms of effect of exposing nano-TiO. Nandini Nalika et al reported the oxidative stress in mitochondria particles into the brain of rat for the evaluation of the toxicity of TNPs. They assessed the potential neurotoxic effect of titanium dioxide nanoparticles (TNPs) that may issue health hazards to mitochondrial brain with the creation of reactive oxygen species (ROS) and have the adverse effects of TNPs on central nervous system (CNS), and therefore TNPs should be precisely consumed. Production of energy and free radicals generate by mitochondria that is a significant origin and these free radicals can induce mitochondrial damage and lastly bring about apoptosis [23, 24].

2.5. Neurotoxicological effects of redox metals, containing iron, copper and cobalt

Lan et al evaluate the neurotoxicity of redox metals, containing copper, cobalt and iron in Parkinson's disease (PD). PD, as a nerve cell disorder in brain, is the gradual loss of dopaminergic neurons that is second most widespread neurodegenerative disease and certainly affected by the oxidative stress. Oxidative stress is one of the conventional reasons and continual vulnerability to contamination of heavy metals and it is affiliated to oxidative stress is concerned in the pathogenesis of PD. It can be mentioned that heavy metal can induce OS could be

involved in the etiological factor and pathogenesis of PD. Totally, neuronal cell death that induced by transition metal normally implicates ROS generation and protein aggregation. Though, ROS may also facilitate metal accumulation may be facilitated by ROS when neurons are under oxidative stress. Deregulation of iron homeostasis can be associated with by concomitant oxidation processes in PD because Iron is an extremely reactive element. Copper have a significant role in neurodegenerative diseases for instance PD because it is a metal in cell division process. Cobalt produce reactive oxygen species (ROS) and induce DNA damage in brain tissues. They propose ROS-generating pathways may be associated with transition metals in PD pathogenesis. Also, in this study, ROS-mediated mechanisms underlying the neurotoxicity of iron, upper and cobalt in PD has examined [9]. Agents for potential therapeutic interventions, mechanism and clinical exhibition, for instance, antioxidants, radical scavengers and metal chelators, recommended to alleviate OS and inhibit incremental decline of dopaminergic neurons in PD [9].

2.6. Neurotoxicological effects of ZnO nanoparticles

ZnO nanoparticles (ZnONPs) are able to cause different changes in brain tissue that represent neurotoxicity happen probably by oxidative stress. The neurotoxicity induced by the elevation in inflammatory cytokines and then reduced glutathione and antioxidant levels. In some study, they examined the neurotoxicity of diverse sized ZnONPs in mouse neural stem cells (NSCs). According to cell viability assay, ZnONPs demonstrated that toxic effects of them on NSCs is dependent to dose, but not dependent to. They reported that at lower concentration, ZnONPs do not induce any cell impairment mechanism but considerably hurt NSCs at a higher dosing. The toxicity on ZnONPs mostly associated with the dissolved Zn^{2+} in the culture medium of cells. There is need for attention during the usage of ZnO nanomaterials to avoid the unintended consequences on human health and environment [25, 26].

Conclusion:

Nanomaterials (NMs) are progressively utilized for biomedical fields that can be applied in the regenerative medicine, the therapy, diagnosis, and monitoring of disease- or drug-induced mechanisms and drug delivery system. Recent studies represent that different nanomaterials have the capacity to penetrate BBB through intravenous injection because of their smaller size and it causes accumulation of them in the brain. It can be mentioned that these nanomaterials can cause intense side effects because they are able to pass the BBB, they can influence the BBB function and brain physiology. This penetrating the BBB can induce neurotoxicity, result in damaging CNS in vivo and Jain diseases. Therefore, there is an urgent prompt for scientists to approach the issues about the neurotoxicity of these nanomaterials and a basis for the extra design and development of the drug delivery system (DDS) using nanomaterials should be arranged for the brain health studies. Nevertheless, the risk of nanomaterials for the BBB and CNS needs more examinations and also should be studied for future trend. Finally, researchers should find some ways to reduce the neurotoxicity effect of nanomaterials that used as a nanocarrier in nanomedicine and drug delivery system.

Conflicts of interest

The authors testify that they have no affiliations with or participating in any association or authority with any financial interest, or non-financial interest in the issue in question or materials argued in this manuscript.

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