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REVIEW PAPER

Differential neurotoxic effects of silver nanoparticles: A review with special emphasis on potential biomarkers

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ABSTRACT

Silver Nanoparticles (AgNPs) have gained considerable interests during the last decade due to their excellent antimicrobial activities. Despite their extensive use, the potential toxicity of these nanoparticles and possible mechanisms by which they may induce adverse reactions have not received sufficient attention and no specific biomarker exist to describe and quantify their toxic effects. Nanoparticles, depending on their physicochemical characteristics and compositions, can interact with vital organs such as the brain and induce toxic effects. A specific concern is that any contact with AgNPs independent of the route of administration is thought to result in significant systemic uptake, internal exposure of sensitive organs, especially in the central nervous system (CNS) and different toxic responses. There are considerable evidences that AgNPs can disrupt the Blood-Brain Barrier (BBB) and induce subsequent brain edema formation. Therefore, it is essential to understand the differential effects of AgNPs on brain cell with especial emphasis on the possible mechanisms of action. Recently, biomarkers are increasingly used as surrogate indicators of toxic responses in biological monitoring due to the inaccessibility of target organs. Moreover, as the most nanoscale contaminants occur at low concentrations, physiological biomarkers may be better indicators of potential impact of nanomaterials than traditional toxicity testing. This review aims to investigate the effects of AgNPs on CNS targets of toxicity and clarify the role of existing biomarkers especially the role of dopamine levels as a potential biomarker of Ag-NPs neurotoxicity.

Keywords: *AgNPs, Biomarker, Dopamine, Neurotoxicity, Silver nanoparticlesCentral nervous system*

INTRODUCTION

In recent years, nanoscale objects are emerging as potential therapeutic and diagnostic tools for a wide variety of diseases, and have also found new applications in medicine, engineering, materials sciences and different industrial applications [1, 2]. An interesting characteristic of an engineered nanoparticle is the possibility of having different physicochemical properties, such as pharmaceutical, chemical, mechanical, magnetic, optical and electrical properties compared with the corresponding bulk materials [3, 4]. Among the various nanotechnology products, silver nanoparticles (AgNPs) are emerging as one of the fastest-growing product categories with the highest degree of commercialization due to their strong antibacterial and antifungal activities [5, 6]. Ag-NPs have become widely employed in medical devices, cosmetics, wound dressing, food containers, and various other consumer products, which may increase the release of nanoparticles to the environment and may cause human exposures and toxic responses [7].

The extensive use of AgNPs raises safety concerns, due to the considerable potential for high exposure in humans and the lack of sufficient information regarding their toxicity [8]. Numerous studies have demonstrated that Ag-NPs administered by inhalation, ingestion, or intra-peritoneal injection are capable of translocating

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into blood circulation and accumulating in several organs like the lung, liver, spleen, kidney and the central nervous system (CNS) [9, 10]. Although various organs can rid themselves of Ag-NPs, these nanoparticles tend to reside for a considerable time and exhibit a longer half-life within the CNS than in other organs, thereby causing neural damages following prolonged exposures [11]. With respect to blood-brain barrier (BBB) function and neurotoxic responses, studies have shown that Ag-NPs can easily cross the BBB and produce damage to the barrier integrity by altering endothelial cell membrane permeability [12].

AgNPs have been also found to impair cell functions and induce cell death in certain cells, such as hippocampal neurons [13, 14]. It seems that an adequate risk assessment of potential neurological effects in response to AgNPs exposure is essential for identifying the possible biomarkers. Yin and colleagues reported that Ag-NPs exposure could induce neurotoxicity *in vitro* through oxidative stress induced apoptosis [15].

More importantly, oxidative stress in neural cells is of particular interest because it is regarded as a key modulator in several neurodegenerative disorders [16]. In support of these findings, it is found that AgNPs with 15 nm diameter may decrease dopamine concentration with an increase in ROS production [17]. An infiltration of the brain with xenobiotics, such as AgNPs, may also lead to inflammation of brain tissues. One study in 2010 has demonstrated that Ag-NPs accumulate with primary rat brain microvessel endothelial cells (rBMEC) in a size-dependent manner and induce the release of cytokines and other inflammatory mediators from the rBMEC cell monolayers [12].

Recently, biomarkers are increasingly used as surrogate indicators of designated events in a biological system due to the inaccessibility of target organs. As most contaminants occur at low concentrations, physiological biomarkers may be a better indicator of potential impact of nanomaterials than traditional toxicity testing [8].

Thus, further studies of oxidative stress associated with gene expression analyses and immunological biomarkers would improve our understanding of the possible mechanisms of neuroinflammation and neurodegeneration associated with Ag-NPs. This review concentrates on studies published between 2000 and 2015 that attempted to detect neurotoxic damages associated by Ag-NPs in laboratory animals and cell lines. The general objective of the current study is to investigate the effects of Ag-NPs on central nervous system and identify potential biomarkers of Ag-NPs neurotoxicity. Improved understanding of such biological effects is needed to guide preventive strategies for the workplaces that use Ag-NPs and risk management guidelines for AgNPs in occupational toxicity.

Mechanisms of Ag-NP neurotoxicity

Ag-NPs interaction with brain cells

Metal-containing nanoparticles have unique properties in their translocation to the systemic circulation and central nervous system (CNS) due to their small size and large surface area [18]. Beside systemic distribution, nanoparticles can be taken up by nerve endings embedded in airway epithelia or in the olfactory bulb, and translocated directly to the CNS [19]. Therefore, there is serious concern that NPs may compromise the CNS which has properties that render it uniquely susceptible to insult. Recent studies have reported that Ag-NPs could gain access to the CNS through the upper respiratory tract *via* the olfactory bulb or through the blood–brain barrier (BBB) and accumulate in various brain regions [11, 20, 21]. Since AgNPs are able to enter the brain, the cells of this organ have to interact with such nanoparticles and with nanoparticle derived metal ions [22].

Brain is composed of two key cell types, neurons and glial cells (including microglia, astrocytes and oligodendrocytes) and also components of the brain vasculature including endothelial cells, smooth muscle cells, and pericytes [23].

Neurons are particularly sensitive to insult because of their high metabolic requirements and long processes (axons up to a meter long, and dendrites) with large surface areas [23, 24]. Recent observations have provided evidence that Ag-NPs can not only reach the brain but also cause a certain degree of brain tissue damage [25]. Therefore, of particular interest is to consider the possible interactions of different brain cells with AgNPs. The first section of present article considers the possible interactions between AgNPs and brain cells.

Ag-NPs interaction with astrocytes

Astrocytes are the most abundant cell type in brain. They have important strategic position among blood capillaries and other brain cells [26].

These cells are the first brain cells that encounter substances that have entered the brain by crossing the blood–brain barrier (BBB) [27]. Astrocytes are considered to play key functions in regulation of gliogenesis, neuronal path finding and regulation of synaptogenesis. They are also involved in the detoxification of xenobiotics and reactive oxygen species, modulation of BBB permeability and act as mediators of neurotoxicity [28, 29].

Therefore, among the different types of brain cells, astrocytes are of particular interest regarding the uptake and the handling of metal-containing nanoparticles such as Ag-NPs [30].

Few *ex vivo* studies tried to detect the consequences of Ag-NPs exposure of brain cells. In an acute (24 h) experiment using mixed primary neuronal cell cultures (astrocytes and neurons) exposed to well characterized 20 and 40 nm Ag-NPs (5–10 ìg/mL), a significant cytotoxic effect was observed at 10 ìg/mL as well as grossly morphological disorganization of the astrocytes but not neurons, and this seems consistent with the finding that Ag-NPs were mainly taken up by astrocytes and not by neurons. At higher concentration such as 20 ìg/mL of Ag-NPs, both cell types exhibited an equally affected morphology. Maximal oxidative stress responses and acute calcium signals were also observed in this concentration [3].

Another study exposed primary cultures of rat astrocytes to 10 ìg Ag/ml of 70 nm PVP-coated Ag-NPs for up to 24 hours. Ag-NPs incubation led to a time- and concentration-dependent accumulation of silver in the astrocytes but it did not affect the cell viability or reduction in cellular glutathione levels. Results of this study suggested the role of coating that help astrocytes to remain viable during long term exposures. In contrast, the incubation of astrocytes for shorter (4 h) exposure with identical concentration of silver as $AgNO_3$, severely compromised the viability of astrocytes. Indeed, the toxic potential of Ag-NPs has been discussed to be caused by Ag+ that is liberated from the nanoparticles [31]. This group also found that endocytotic processes appear to be predominantly responsible for the uptake of Ag-NPs into the target cells [31, 32].

Despite above information, one recent study has shown that cultured astrocytes are highly efficient to accumulate Ag-NPs in a time, concentration and temperature dependent manner.

These cells appear neither to be damaged by the acute exposure to Ag-NPs nor by chronic presence of large amounts of accumulated NPs. Although metal ions are liberated from accumulated Ag-NPs in astrocytes, Ag-NP released Ag+ ions appear not to be exported from the cells but are rather stored in metal storage proteins such as metallothioneins (MTs) [30]. The efficient accumulation of large amounts of metal-containing NPs and the upregulation of proteins that safely store Ag-NPs suggest the specific protective role of astrocytes against the potential toxicity of Ag-NPs in the brain. Table 1. shows the toxic effects of Ag-NPs on astrocytes.

Table 1. Toxic effects of Ag-NPs on Astrocytes

Study	Size of AgNP	Target cell	Considered factors	Mechanism of toxicity	Biomarker
Eva M Luther (2011)	70 ± 20 nm	Cultured primary astrocytes	Coating,time-, concentration- and temperature-dependent.	GSH depletion , Decrease in cellular LDH activity or LDH reduction	Endocytosis inhibitors(MβCD, Chloroquine, 3-methyladenine, Wortmannin,Amiloride, EIPA, Chlorpromazine)
Luther EM (2012)	75 ± 20 nm	Cultured primary astrocytes	Concentration-dependent	Metallothioneins upregulation	Metal-binding metallothioneins (MTs)
Andrea Haase (2012)	20 and 40 nm	Astrocytes	Size-dependent.	Acute calcium response, ROS formation	HO-1(a well-established marker of chemical-induced oxidative stress), protein carbonyls (a sensitive indirect endpoint of ROS formation)

Ag-NPs interaction with neurons

The effects of nanoparticles in neural cells should be carefully analyzed because the neurons damage plays critical role in the etiology of some neurodegenerative disorders such as Parkinson's and Alzheimer's diseases [35]. Neurons can be defined as nerve cells that, together with neuroglial cells, constitute the nervous tissue making up the nervous system. These cells are electrically excitable brain endothelium to transmit information through chemical and electrical signals via synapses and contact with pericytes and perivascular astrocytes [33]. In addition, neuron synaptic transmission and neuron cell membrane with the ionic channels for Na^{+}þ, K^{+}, $Ca^{2þ+,}$ þand Cl^{-} may provide an important route of entry for nanoparticles [22]. Moreover, these cells are particularly sensitive to insult because of their high metabolic requirements [34]. In PC12 cells, a well-established model of neuronal development, high concen-trations of Ag-NPs disrupt the cell function [17]. An *in vitro* study conducted with 20 nm Ag-NPs to examine the potential hazardous effects of Ag-NPs with cortical neurons, demonstrated that in well-established neurons, Ag-NPs not only inhibit the sprouting of neuronal branches and elongation of neurites, but also caused degeneration of neuritic processes or aberrant aggregations of cell bodies. Noticeably, this study provided the first morphological and cellular evidence that exposure to 20 nm Ag-NPs resulted in a reduction in synaptic proteins, cytoskeletal integrity, mitochondria functionality and cell viability in a dose-dependent manner [36]. Several *in vitro* reports have also demonstrated that Ag-NPs can impair cell functions and even induce cell death in certain cells, such as hippocampal neurons [13, 37]. Ag-NPs exposure, leads to Ag accumulation in the adult rodent brain, altering the expression of genes involved in neuronal func-tion in PC12 cells [44]. Kim et al., reported that silver NPs can induce significant cytotoxicity in cultured cerebral cortical neurons in a dose-dependent and time-dependent manner. The viability of cortical neurons significantly decreased at the tested time points after treatment with Ag-NPs at concentrations of }"2 ìg/mL. The results of this study suggested that Ag-NPs may induce the apoptosis of cortical neuronal cells by enhancement of intracellular ROS generation [45]. Liu et al., also found that Ag-NPs (10 ìg/mL) may alter the potential of hippocampal CA1 neurons by modulation of sodium channels [14].

Yin and colleagues have shown that Ag-NPs at 10 ìg/mL for 24 h produced significant cytotoxicity in rat cerebellum granule cells (CGCs), but had little effect on the cell membrane integrity. Ag-NPs could induce CGCs death through apoptosis and the apoptotic proportion elevated with the increase in exposure dose [15].

They also found that oxidative stress was the expected mechanism for apoptosis as Ag-NPs could induce oxidative cell damage by inducing ROS generation, depleting GSH levels and disturbing the calcium homeostasis [15, 38, 39]. Additional evidences demonstrated that several kinds of nanomaterials such as ZnO, TiO_2, Au and silica could disturb the intracellular calcium homeostasis [40-43]. Importantly, the presence of Ag-NPs in neuronal cells after subcutaneous exposure directly offered the possibility that Ag-NPs exert influence over biological functions in the brain [15]. Table 2. shows the toxic effects of Ag-NPs on Neurons.

Ag-NPs interaction with endothelial cells

There have been few numbers of publications focusing on the potential neurotoxicity of AgNP on endothelial cells. AgNPs have been shown to be able to migrate into the brain *via* the olfactory nerve after nasal inhalation [19]. Thus, it is thought that Ag-NPs should be evaluated in terms of their potential effects on important constituents of the blood brain barrier (BBB) namely microvascular endothelial cells. Recently, a study from Gross et al., demonstrated that citrate-coated Ag-NPs led to membrane damage and impair colony formation of rat brain endothelial (RBE4) cells. Assessment of membrane damage showed that exposure to 10 nm Ag led to a strong reduction of dye uptake compared to untreated cells. The effect was considered to be dependent on particle surface area, particle size, dose and exposure time [46]. Similarly, Trickler et al., used RBE4 cells as a model to examine the cellular accumulation, changes in pro-inflammatory mediators and changes in morphology and permeability following exposure to PVP-coated AgNP in sizes of 25, 40 and 80 nm. It was observed that Ag-NPs accumulated in the cells in a size-dependent manner with less accumulation observed for the 80 nm AgNP. Therefore, Ag-NPs led to significant cytotoxicity and caused the release of cytokines and other inflammatory mediators from the cell monolayers [12]. Table 3. shows the toxic effects of Ag-NPs on endothelial cells.

Table 2. Toxic effects of Ag-NPs on Neurons

Study	Size of AgNP	Target cell	Considered factors	Mechanism of toxicity	Biomarker
Neural Cells					
Saber M.Hussain (2006)	15 nm	PC12, Hippocampal	Concentration-dependent DA Depletion (Ag 15 nm only significantly reduced DA and DOPAC at concentrations of 50*mg*/ml, Ag 15 nm displayed a significant depletion of DA only at a highly toxic dose of 50 mg/ml)	Cell function disruption	Reactive oxygen species (ROS), dopamine levels
Fenglian Xu(2013)	20 nm	Cortical neurons	Dose dependent	Morphological and functional disorders, decreased viability	Synaptic proteins, synaptophysin and PSD-95 (distinct punctate labeling with a presynaptic marker of synaptophysin and a postsynaptic marker of PSD-95). Cytoskeletal proteins (e.g. β-tubulin and F-actin), dissolution of synaptic proteins (e.g. synaptophysin and PSD- 95)
Nuoya Yin(2013)	22.8 $\pm$0.7 nm to 25.9 $\pm$0.3 nm in culture medium and from 1.7$\pm$1.1 nm to 24.4 $\pm$0.6 nm in aqueous solution	Rat cerebellum granule cells (CGCs)	Dose dependent, 10 μ g/mL for 24 h	Cell death , apoptosis induction,ROS generation,GSH depletion,calcium homeostasis disruption	Caspase-3
Andrea Haase(2012)	20 and 40 nm	Neurons (Primary cultures of neurons from cortex)	Size-dependent	Calcium dysregulation and ROS formation	HO-1 (a well-established marker of chemical-induced oxidative stress), protein carbonyls (a sensitive indirect endpoint of ROS formation)
Zhaowei Liu(2010)	223.9 nm	Hippocampal CA1 neurons	Voltage- Gated Potassium Currents	Inhibition of K1 currents, increased Ca21 influx, neuronal dysfunction and death	Not determined
Chin-Lin Huang (2015)	3-5 nm	Neuron N2a cells	Size dependent	Accelerate Aβ1–40 and Aβ1–42 generation and deposition, gene expression of CXCL13, MARCO and GSS, L-1β secretion, oxidative stress, LDLR and NEP reduction	Chemokine 13 (CXCL13) and cytokine L-1β
Sung-Hwan Kim (2014)	6.45±2.55 nm	Cerebral cortical neurons	Time and dose dependent	ROS generation, apoptosis induction and neuronal viability reduction	Caspase-3
Christina M Powers (2011)	10 and 50 nm	PC12 cells	Size and coating	Impaired DNA synthesis, ROS generation, impaired differentiation	Acetylcholine and dopamine levels

Table 3. Toxic effects of Ag-NPs on endothelial cells

Endothelial cells					
William J. Trickler (2010)	25, 40, or 80 nm)	Rat brain microvessel Endothelial cells (rBMEC)	Size and time-dependent	Morphological changes, release of pro inflame-matory mediator and increased permeability in rBMEC	Cytokine (TNFa, IL-1b, and IL-2)
Susann Grosse (2013)	10, 50 and 100 nm	Endothelial (RBE4) cells or RBE4 cell line	Size, surface area, dose and exposure time	Membrane damage and impair colony formation of RBE4 cells	Not determined

AgNPs interaction with blood brain barrier

The blood–brain barrier (BBB) is a separation of circulating blood and cerebrospinal fluid (CSF) maintained by the choroid plexus in the CNS. The BBB is formed by endothelial cells that line cerebral microvessels and that are closely connected by tight junctions which prevent uncontrolled paracellular flux [22]. Under normal conditions, the BBB regulates the microenvironment of the brain by selectively regulating transport of molecules and cells in and out of the brain. Small-sized particles have better mobility and it is supposed that the transportation of engineered NPs across the BBB is possible either by carrier-mediated endocytosis or by passive diffusion [47]. Until now, the effects of Ag-NPs on barrier integrity, permeability and tight junction formation have been evaluated in a very limited number of studies. One research focusing on the interaction between Ag-NPs and BBB has shown functional disruption of the BBB and subsequent brain edema formation. For instance, Sharma et al., investigated the effect of nanoparticles derived from Ag, Al and Cu (50–60 nm) on BBB permeability in relation to brain edema in a rat model. They suggested that nanoparticles from metals when administered systemically are able to induce breakdown of the BBB permeability, depending on the route of administration and the type of nanoparticles. Results from this study showed that administration of Ag and Cu nanoparticles intravenously or super fused over the cortical surface profoundly induced the breakdown of the BBB to protein tracers compared to Al nanoparticles [48]. Although, the mechanisms by which engineered nanoparticles influence the BBB function are still not well-known, it appears that nanoparticles depending on their characteristics may induce oxidative stress within the brain microvessels [49, 50]. Moreover, Cramer et al., compared the effects of two Ag-NPs with different surface modifications (ethylene oxide and citrate) and surface charges (Ag citrate-NP are more negatively charged) on cells of the BBB and blood-CSF barrier *in vitro*. Cytotoxic effects of the silver NPs led to an increased barrier permeability and nanoparticle uptake into the brain. They also found that the more negatively charged Ag citrate-NPs exhibited a less pronounced effect on the BBB and the blood-CSF-barrier *in vitro* [51]. Trickler and colleagues have also conducted an *in vitro* study in a primary BBB model. They observed a size-dependent pro-inflammatory response through the release of TNF-α, Il-1β and prostaglandin E2 and an increase in BBB permeability after exposure to different sizes of Ag-NPs [12]. Interestingly, a study by Hanada et al., elucidated the permeability of silica NPs through the blood–brain barrier using a cell-based *in vitro* BBB model. It is found that the 30 nm silica nanoparticles, especially at the high concentration, were transported through the BBB model, mirroring the same result reported in an animal model [52]. The mechanism of metal-based brain NP uptake across the intact BBB is believed to be transcytosis through the brain microvascular endothelial cells (BMECs) [23]. In support of these findings, Tang and colleagues demonstrated AgNP-induced BBB destruction, astrocyte swelling and neuronal degeneration in a rat model [53].

Biomarkers of neurotoxicity

The best way to minimize the toxic effects of engineered nanomaterials is to provide preliminary toxicity guidelines for the nano-manufacturing industry. Biological monitoring (BM) can be used as a valid tool in the practice of occupational safety and health with the purpose of identifying potential hazards of new and emerging chemicals, including

manufactured nanoparticles [54]. Biomarkers are regarded as early, preferably reversible, biological signs which are indicative of an actual or potential condition of exposure [55].

Existing research has shown that several nanoparticles such as silver are capable of crossing the blood brain barrier (BBB) and enter the brain [51]. Specifically, the deposition of silver nanoparticles in the brain can stimulate oxidative stress, inflammatory responses, and pathological change. Dopaminergic neurons can be specifically targeted *in vitro* by a wide spectrum of nanoparticles, including Mn, Ag, or Cu NPs [56]. Therefore, there is a need for the selection of potential biomarkers of early effects to be used in human studies.

Biomarkers of oxidative stress

The brain is particularly susceptible to oxidative stress-induced damage because of its high oxygen consumption, relatively high concentration of iron and ascorbate to carry out the radical generating Fenton reaction, and relatively low concentration of antioxidants and antioxidant enzymes [57]. Glutathione peroxidase (GPx) is one of the main antioxidant enzymes involved in protecting the cells against oxidative stress and the glutathione redox cycle is a major source of protection against mild oxidative stress [58]. Among neurodegenerative diseases, the oxidative stress has been strongly implicated in Parkinson's disease [59]. Recent studies have provided evidence that metal-based NPs including silver act as catalyst and could produce reactive oxygen species (ROS) in the presence of oxygen, which is considered to be a mechanism of toxicity and genotoxicity [60]. It is presumed that surface oxidation of Ag-NPs, upon contact with cell culture medium or proteins in the cytoplasm, liberated Ag^+ ions that could intensify the toxicity. Reactions between H_2O_2 and Ag-NPs are believed to be one of the main factors causing Ag^+ ions to release *in vivo* [61].

A possible mechanism involves:

$$2Ag + H_2O_2 + 2H^+ \longrightarrow 2Ag^+ + 2H_2O_2$$

$$E = 0.17\ V$$

There have been numerous studies demonstrating the induction of ROS following exposure to Ag-NPs. In a recent study, cell death and DNA damage induced by Ag-NPs were prevented by Tiron and dimethyl thiourea, which scavenged superoxide anions (O_2^-) and H_2O_2, respectively, indicating the role of ROS in AgNP-induced cell death and DNA damage [62, 63]. Dziendzikowska and colleagues indicated that Ag-NPs increased ROS generation and hemeoxygenase1 (HO-1) protein expression to cause neuronal oxidative damage and directly interfered with calcium responses in primary mixed neural cells [64]. In addition, glutathione metabolism plays a major role of protecting cell from oxidative stress, and their gene expression related to oxidative stress are significantly altered in the caudate, frontal cortex and hippocampus of male C57BL/6N mice after administered Ag-NPs (25 nm) [65]. Importantly, glutathione synthetize (GSS) can synthesize glutathione (GSH) to inhibit oxidative stress and prevent cellular damage from free radicals and peroxides [66], and Ag-NPs exposure possibly alters GSS gene expression [67]. In another study, Low dose (3 mg/kg) and high dose (30 mg/kg) of Ag-NPs were given to rats for 14 days. The rats treated with Ag-NPs showed significantly increased ROS in their hippocampal homogenate [68]. Investigation on the other key player in AgNP-induced apoptosis showed that Ag-NPs could induce oxidative cell damage in rat cerebellum granule cells (CGCs) through evoking ROS, which was further validated by depletion in GSH levels, as previous reports showed that nanomaterials could provoke oxidative stress, a common mechanism of cell damage [15]. Under *invivo* conditions, Hritcu et al., evaluated the effects of nanoparticles size (23 and 29 nm) and structure on rat memory function. They found that AgNPs may induce an impairment of memory functions by increasing oxidative stress in the brain [69]. Furthermore, Rahmant et al., evaluated the effects of silver nanoparticles (25 nm) on gene expression in different regions of the mouse brain. Due to the Ag-NPs insult, mouse oxidative stress and antioxidant defense genes were differentially expressed in the frontal cortex, caudate and hippocampus of mice. Specifically, Fmo2 gene was up-regulated significantly in the frontal cortex, caudate and hippocampus. It has been shown that the Fmo gene was involved in the oxidative metabolism of various xenobiotics and catalyzed the oxidation of reduced glutathione (GSH) to glutathione disulfide [70]. Thus, up-regulation of Fmo2 by Ag-NPs (25 nm) may disturb GSSG/GSH balance and cause neurodegeneration [65]. The quantification of GSH levels has been proposed as a biomarker of oxidative stress [71]. In another experiment, the effect of Ag-NPs on hippocampal

synaptic plasticity and spatial cognition was investigated in rats and followed with the research on their possible mechanism. The results showed that the quantity of ROS in hippocampal homogenate increased significantly in both low-dose and high-dose groups, which may be attributed to the neural damage caused by Ag-NPs [68].

Noticeably, vitamin E (VE) is the most important lipid-soluble antioxidant that protects the brain from oxidative damage [72]. Recently, Liu et al., hypothesized that VE could protect against reactive oxygen species (ROS)-induced toxicity following Ag-NPs administration [73]. These findings indicate that oxidative stress and elevated levels of oxidatively altered biomolecules are important intermediates that may be useful markers for characterizing the potential hazards of Ag-NPs exposure.

Biomarkers of inflammation

Microglia are the immune cells within the CNS, but they are complemented by CNS-derived macrophages that are located in the meninges, choroid plexus and perivascular space. The number of microglia is limited, constituting 20% of the total glial cell population in the normal brain [74]. When these cells sense injury or a foreign (infectious) agent, a network of activation pathways is induced in microglia, resulting in an altered microglial morphology, intense respiratory metabolism and the expression and release of immune molecules including chemokines, cytokines, (IL-1â, IL-6 and TNF-a) [75]. It has been demonstrated that the activation of microglia may respond sensitively to even minor pathological challenges that affect the CNS [76]. One of the important targets for these inflammatory mediators is the isolated primary cerebral microvessel endothelial cells (rBMEC) and cerebral microvasculature have been well correlated with event cascades that release pro-inflammatory cytokines [12]. It has been also shown that TNF or IL-1â increase brain microvascular permeability [77]. High levels of cytokines upon treatment with engineered nanoparticles are usually associated with toxicity, adverse reactions and low therapeutic efficacy, as will be discussed later. Therefore, cytokines might be utilized to partially predict the nanoparticle immunotoxicity [78]. Several studies have demonstrated that Ag-NPs can distribute systemically, cause inflammation and cytokine responses. As CXCL13 and MARCO genes are involved in immune mediatory responses, exposure to silver nanoparticles may change their gene expression [66]. For example Huang et al., has recently reported that Ag-NPs (3–5 nm) can enter mouse neural cells to induce pro-inflammatory cytokine secretion and increase Aâ amyloid deposition in response to the changes of gene expression in inflammatory response, oxidative stress and Aâ degradation [67]. As mentioned before, Ag-NPs can induce inflammation to microves-sel endothelial cells of the blood brain barrier (BBB) in a dose, time, and size-dependent manner. Importantly, they can trigger cytotox-ic responses and stimulate the expression of immune-relat-ed cytokines, such as IL-1â, IL-2, tumor necro-sis factor (TNF-á), and prostaglandin E2 [79]. The responses to silver NPs were shown by the increasing permeability of biological barrier and the reducing integrity of endotheli-al cell monolayer [12]. Understanding the use of cytokines as biomarkers of undesirable immuno-stimulation associated with engineered Ag-NPs is emerging as an essential component of nanoparticle safety testing.

Dopamine as a biomarker

Dopamine (DA) is a compound of great biomedical interest, playing significant role in the functioning of central nervous system [80]. DA is a major neurotransmitter in the brain's neural circuits and its depletion resulted in movement disorders that were characterized by Parkinson's disease [81]. Abnormal dopaminergic transmission has also been involved in Huntington's disease and neuroendocrine disorders [82]. Dopaminergic cells in the brain are known to express the dopamine transporter (DAT), which regulates extracellular dopamine concentration by mediating its reuptake and maintains proper intracellular dopamine stores [83]. Hussain et al., have shown that manganese (Mn) NPs (40 nm) induce the depletion of dopamine and its metabolites in a dopaminergic neuronal cell line (PC12); and such depletion is accompanied by an increase in reactive oxygen species (ROS) production. This study also demonstrated that Ag-NPs (15 nm) moderately decrease dopamine content with an increase in ROS production [17]. As a follow-up, Wang and colleagues further explored the mechanisms of Cu (90 nm), Mn (40 nm) and Ag (15 nm) NPS induced dopaminergic toxicity by examining the expression changes of 11 dopaminergic system-related genes in PC12 cells [56]. The results indicated that these nanoparticles produced significant

alterations in 11 genes associated with the dopaminergic system in PC12 cells. In this study, the treatment with Ag NPs (15 nm) down-regulated the expression of Gpx1 in PC12 cells. The decrease in Gpx1 gene expression after Ag exposure in these cells clearly demonstrated that these NPs affected the glutathione system and generated oxidative stress. However, after exposure to Ag-NPs (25 nm), the Gpx enzyme was inhibited and was not available to hydrolyze free radicals, leading to oxidative stress and ROS formation. which has been shown earlier *in vitro* and *in vivo* [65, 84]. In female rats, it has been reported that 14 nm Ag-NPs (4.5 and 9 mg AgNP/kg/day) increased the dopamine concentration in the brain following 28 days of oral administration. In contrast, the dopamine concentration in the brain decreased by Ag-NPs (14 nm, 2.25 and 4.5 mg/kg/day) following a 14-day exposure [25]. These diverging results suggested that an early decrease in dopamine level induced by Ag-NPs is followed by a compensatory increase by day 28. Likewise, an initial increase in manganese concentration induced dopamine brain concentration (30–90 days) and was followed by a normalization (120–180 days) of the dopamine concentration [85]. It should be noted that the decrease in brain dopamine concentrations observed following 14 days of Ag-NP administration could be explained by an increase in apoptosis of dopaminergic neurons. According to findings in Parkinson's disease, there is evidence for an initial increase in the dopamine brain concentration followed [86]. According to Hussain et al., Ag-NPs (5×10^{-5} g/ml) reduced dopamine concentration, and the nanoparticles of Ag were found probably more toxic than that of manganese (Mn) nanoparticles in a neuroendocrine cell line (PC-12 cells) [17]. Taken together, these data support the possibility that the effects of nanoparticles on dopamine brain concentrations can vary depending on either the length or level of the exposure. It has been indicated that voltage-gated sodium currents determined a large number of neuronal properties, such as influencing action potential generation, the propagation of action potentials to synapse terminals, or the local depolarization of neuron, and also are known to play a key role in transport of neurotransmitters including dopamine, norepinephrine, and serotonin [87]. Recently, a study by Zhaowei et al., showed that only Ag-NPs (10-5 g/ml) reduced the amplitude of voltage-gated sodium current (INa), which may result in decrease in intracellular Na^+ concentration due to decreased Na^+ inffux [14]. To assess early effects of chemicals targeting the dopaminergic systems, a neurochemical and neuroendocrine approach based on surrogate biomarkers has been developed [88]. Finally, among all the selected biomarkers, dopamine could be selected as a probable biomarker for neurotoxicity of silver nanoparticles.

Conclusions and future prospects

With the rapid and extensive research is now underway into the design of novel nanomaterials, it is critical that attention be directed toward their potential neurotoxicity. Much work has been done with cells in culture as proof of the concept that AgNPs interact with brain cells. However, less work has been done testing the possible neurotoxicity of these nanoparticles *in vivo*. This review provided evidence that Ag-NPs cause the generation of oxidative stress and an impairment of the antioxidant enzyme glutathione peroxidase in rat brain. Silver nanoparticles treatment also caused a significant decrease in the levels of neurotransmitters such as dopamine, indicating a possible change in the behavior of the treated animals. Moreover, evaluation of the immunotoxicity of nanoparticles, for example, by measuring the levels of cytokines or other immune-indicators, is of particular importance for their clinical safety. Combination of several markers might also be useful to understand the underlying mechanisms of neurotoxicity induced by silver nanoparticles. To advance the risk assessment process, future *in vitro* studies should be designed with exposure conditions relevant to NPs concentrations that might be achieved *in vivo*. Another topic that has been minimally addressed (if at all) includes adverse effects of Ag-NPs on spinal cord and peripheral nervous system (PNS). Therefore, understanding of the neurotoxic effects of silver NPs would help in the development of safety guidelines by authorities to promote nanotechnology for applications without hazard. (NR Panyala).

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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