Impact of nanoparticles on neuron biology: current research trends

Abstract: Nanoparticles have enormous applications in textiles, cosmetics, electronics, and pharmaceuticals. But due to their exceptional physical and chemical properties, particularly antimicrobial, anticancer, antibacterial, anti-inflammatory properties, nanoparticles have many potential applications in diagnosis as well as in the treatment of various diseases. Over the past few years, nanoparticles have been extensively used to investigate their response on the neuronal cells. These nanoparticles cause stem cells to differentiate into neuronal cells and promote neuronal cell survivability and neuronal cell growth and expansion. The nanoparticles have been tested both in in vitro and in vivo models. The nanoparticles with various shapes, sizes, and chemical compositions mostly produced stimulatory effects on neuronal cells, but there are few that can cause inhibitory effects on the neuronal cells. In this review, we discuss stimulatory and inhibitory effects of various nanoparticles on the neuronal cells. The aim of this review was to summarize different effects of nanoparticles on the neuronal cells and try to understand the differential response of various nanoparticles. This review provides a bird’s eye view approach on the effects of various nanoparticles on neuronal differentiation, neuronal survivability, neuronal growth, neuronal cell adhesion, and functional and behavioral recovery. Finally, this review helps the researchers to understand the differential roles of nanoparticles (stimulatory and inhibitory) in neuronal cells to develop effective therapeutic and diagnostic strategies for neurodegenerative diseases.

Keywords: nanoparticles, neuron biology, neuroprotection, neurotoxicity

Introduction of nanoparticles

Nanoparticles or nanomaterials are one millionth of a millimeter, ~100,000 times smaller than the diameter of a human hair. Most nanoparticles are too small to be seen with the naked eye and even with conventional lab microscopes. Nanoparticles can be derived from both natural and synthetic sources. Over the past few years, synthetically derived nanoparticles generated tremendous interests and based on the chemical compositions, nanoparticles can be broadly classified into two major classes such as organic materials, which are liposomes, dendrimers, carbon nanotubes, emulsions, and other polymers, and inorganic materials, which include metals.1–3 Nanoparticles can be synthesized in different sizes (1.0–500 nM) and shapes (cones, cubes, rods, tubes, and shells).4–6

There are various applications of nanoparticles in biotechnology, biosensing, catalysis, magnetic fluids, separation techniques, energy storage, and environmental modification7–12 and also in biomedical field, especially in diagnostics, and drug or gene delivery.13–19 Interestingly, nanoparticles have been extensively used as drug carrier systems for therapeutic molecules with the primary aim to improve the therapeutic effect and decrease their side effects and drug/gene delivery.20–23 One of the major attributes...
of nanoparticles is their precise targeting, biocompatibility, bioavailability, and multifunctional capabilities. In the recent past, several attempts have been made to study the effect of different classes of nanoparticles on cancer cells. In addition, interests have also been generated to study the effects of nanoparticles on neurons and there are several reports that suggest that nanoparticles promote neuronal differentiation, and neuroprotection studied in both in vitro and in vivo conditions. To get better therapeutic results, various types of nanoparticles have been studied in neurons, and among those, carbon-based nanoparticles are mostly reported, followed by gold and silver nanoparticles (AgNPs). Despite having many beneficial properties, nanoparticle also raises few health hazard and toxicity issues. To better understand the safety profile of the nanoparticles, several attempts have been made to know whether nanoparticles cause any side effects or toxic effects. It has been shown that nanomaterials possess highly activated surfaces that are capable of inducing carcinogens, mutagens, or health hazard responses. Furthermore, it has been reported that carbon nanotubes induced fibrogenesis on nanostructured substrates. Moreover, nanoparticles are 100 times smaller than normal red blood cells, which increase the potential for interaction, and there is evidence that nanoparticles interact with proteins, DNA, lung cells, and viruses. The current assumption is that nanoparticles such as silica featured as hydrophilic, hydrophobic, or even amphiphilic that can be taken up by human membranes may pose serious threats. Hence, understanding nanoparticles’ interaction with living cells and other biologic systems, especially with central nervous system (CNS), is critical. Nanoparticles have potential functionality and toxic effects on human neuronal cells because they can pass through biologic membranes. It is known that the biologic half-life of silver in the CNS is longer than that in other organs, suggesting that there may be some significant physiologic functions, consequences, and risks to the brain because of prolonged exposure. In addition, effects of nanoparticles on the blood–brain barrier (BBB) were also evaluated, and it was found that administration of Ag, Cu, or Al/Al₂O₃ nanoparticles showed disrupted BBB function and induced brain edema formation. Moreover, AgNPs induced BBB destruction and astrocyte swelling and caused neuronal degeneration. In the present review, we have discussed various nanoparticles and their impacts on the neuron’s biology and tried to evaluate their responses (stimulatory or inhibitory), which were studied in both in vitro and in vivo models, respectively.

**Stimulatory effect of nanoparticles on neuronal cells**

Nanoparticles have tremendous capabilities to stimulate neuronal cells toward neuronal cell proliferation, axonal growth, neuronal cell adhesion, and neuroprotection (Figure 1). It has been demonstrated that nanoparticles can also differentiate stem cells into neuronal cells. The nanoparticles with different shapes such as nanotubes, nanofibers, nanocone, and nanoemulsion have been used to test their effects on the neuronal cells. For example, nanotubes and nanofibers promoted neuronal regeneration, activated hippocampus neurons activities, neurons growth, and neuronal protection. In addition, there are few reports about use of nanoscaffold,
nanocomplexes, and nanomembrane in neuron regeneration and neural tissue reconstruction.\textsuperscript{65–67} The stimulatory effects of some of the nanoparticles are diagrammatically depicted in Figure 2. Like shapes of the nanoparticles, size of the nanoparticles is also important in inducing biologic response.\textsuperscript{68} For example, nerve growth factor (NGF)-encapsulated chitosan nanoparticles with size 80–90 nM caused differentiation of canine mesenchymal stem cells into neurons,\textsuperscript{69} whereas calcium phosphate–lipid nanoparticles with size 30 nM caused neuronal differentiation.\textsuperscript{70} In another report, it has been found that prodrug nanoparticles with 50 nM size improved neuronal survival.\textsuperscript{71}

Nanoparticles are either used alone or in combination or conjugation with other molecules to achieve better response on the neuronal cells. It is not easy to discuss each nanoparticle in detail, so we briefly describe the impact of nanoparticles on neurons. For example, it was reported that the use of the nanoparticle triiodothyronine along with retinoic acid caused neuronal differentiation.\textsuperscript{72} In addition, treatment of triiodothyronine along with retinoic acid also caused a significant increase in the expression of neural lineage-specific markers. Moreover, treatment of triiodothyronine also caused 10-fold increase in the gene expression of β-III-tubulin, and five-time increase in microtubule-associated protein 2 gene expressions.\textsuperscript{72} It was reported that three-dimensional poly(3,4-ethylenedioxythiophene) doped with hyaluronic acid nanoparticles conjugated with chitosan or gelatin matrix caused neuronal cell differentiation.\textsuperscript{73} In another study, it was reported that poly(3,4-ethylenedioxythiophene) coated with microelectrodes have significantly reduced neuronal death and neuronal damage as compared to noncoated controls.\textsuperscript{74} Carbon dots (C-dots), a class of fluorescent nanoparticles with pure carbon core, have great bioanalytical potential. In addition, the application of multifunctional fluorescent C-dots caused neuronal differentiation in adult stem cells.\textsuperscript{75} In another study, it was reported that fluorescent C-dots (40–800 μg/mL) caused reduction of acidification of synaptic vesicles and increased the ambient level of the neurotransmitters.\textsuperscript{76}

Interestingly, it was reported that treatment of NGF-loaded heparinized cationic solid lipid nanoparticles (HCSLNs) caused differentiation of induced pluripotent stem cells (iPSCs) into neuronal cells.\textsuperscript{77} In addition, presence of neuron-specific staining in differentiated neuronal cells confirmed that NGF-loaded HCSLNs caused neuronal cell differentiation.\textsuperscript{77} Recently, it was reported that traceable microRNA-124-loaded nanoparticles, efficiently delivered into neural stem or progenitor cells, promoted neuronal differentiation and maturation.\textsuperscript{79} Similarly, it was reported that nanocrystalline glass-like carbon (NGLC) can induce neuronal differentiation. It was reported that NGLC caused differentiation of the dopaminergic neurons derived from the substantia nigra of the transgenic mouse embryo’s brain.\textsuperscript{79} Nanoparticles caused not only the neuronal differentiation but also the formation of new cells. For example, treatment of nanoparticles caused an increased formation of daughter neuronal cells.\textsuperscript{80} In another report, it was demonstrated that polyvinylidene fluoride and poly vinylidene fluoride-co-trifluoroethylene or BaTiO3

![Figure 2 Stimulatory effect of nanoparticles on neuronal cell tested in animal models.](https://www.dovepress.com/)

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that treatment of RA-NP protected endothelial cells from ischemia effect. Enhanced vascular regulation of neural stem cell and differentiation after ischemia. Administration of triiodothyronine in a rat model of ischemic stroke was reported to cause a 34% decrease in tissue infarction and a 59% decrease in brain edema. In another study, it was reported that cerium oxide nanoparticles caused opposite and damaging action on the neuronal cells. These nanoparticles with different shapes, sizes, and chemical compositions improved nerve regeneration, neuronal recovery, neuronal signaling, neuroprotection, and neurogenesis in various animal models. These nanoparticles were also able to improve functional and behavioral recovery of the motor functions in the animal models of Parkinson’s disease and spinal cord injury.

**Inhibitory effect of nanoparticles on neuronal cells**

Despite having therapeutic potentials, nanoparticles pose safety concerns. There are few nanoparticles, which are also reported to have inhibitory effects on the neuronal cells. These nanoparticles caused opposite and damaging action on the neuronal differentiation. The inhibitory effect on the neuronal differentiation is diagrammatically depicted in Figure 3. It was reported that cerium oxide nanoparticles displayed antioxidant properties in both in vitro and in vivo conditions. The stimulatory effects of nanoparticles caused an increased neuronal cell differentiation and promoted nerve regeneration, hippocampal neuron activity, cell viability, neuronal growth and cerebral neuronal induction, and gene expression in nigral dopaminergic neurons. They also promoted neuronal growth, axonal guidance, Schwann cells’ guidance, neural tissue reconstruction, neuronal–glial interaction, neurogenesis, and neuroprotection. These nanoparticles with different shapes, sizes, and chemical compositions improved nerve regeneration, neuronal recovery, neuronal signaling, neuroprotection, and neurogenesis in various animal models. These nanoparticles were also able to improve functional and behavioral recovery of the motor functions in the animal models of Parkinson’s disease and spinal cord injury.
Table 1 List of various nanoparticles with stimulatory effects on neurons

<table>
<thead>
<tr>
<th>Name of nanoparticles</th>
<th>Activities measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanofibrous scaffold</td>
<td>Promoted nerve regeneration85</td>
</tr>
<tr>
<td>Carbon nanotube</td>
<td>Promoted hippocampal neurons’ activity97</td>
</tr>
<tr>
<td>Nanofibers</td>
<td>Promoted nerve regeneration66</td>
</tr>
<tr>
<td>Gold nanotubes</td>
<td>Promoted nerve regeneration39</td>
</tr>
<tr>
<td>Silica</td>
<td>Increased cell viability95</td>
</tr>
<tr>
<td>Gold nanocone</td>
<td>Increased neuronal growth100</td>
</tr>
<tr>
<td>BNDF-PS80-PBCA</td>
<td>Promoted neuronal differentiation101</td>
</tr>
<tr>
<td>Gatofloxacin</td>
<td>Promoted cerebral neuronal induction102</td>
</tr>
<tr>
<td>NTS-polyplex nanoparticle</td>
<td>Promoted gene expression in nigral dopaminergic neurons103</td>
</tr>
<tr>
<td>Core–shell nanoparticles</td>
<td>Promoted nerve regeneration104</td>
</tr>
<tr>
<td>Poly(lactide-co-glycolide) nanoparticles</td>
<td>Promoted nerve regeneration105</td>
</tr>
<tr>
<td>Electrospun fiber scaffolds</td>
<td>Promoted neuronal growth60</td>
</tr>
<tr>
<td>Magnetic nanoparticles</td>
<td>Reversed Parkinson’s syndrome106</td>
</tr>
<tr>
<td>Zero valent zinc nanoparticles</td>
<td>Promoted neuronal proliferation107</td>
</tr>
<tr>
<td>Curcumin–docosahexaenoic acid-loaded carriers</td>
<td>Promoted neuronal survival45</td>
</tr>
<tr>
<td>Graphene and carbon nanotube</td>
<td>Promoted neuronal biocompatibility108</td>
</tr>
<tr>
<td>Active microcarriers</td>
<td>Promoted neuronal differentiation109</td>
</tr>
<tr>
<td>Gelatin/neroceria nanocomposite fibers</td>
<td>Promoted neuronal regeneration94</td>
</tr>
<tr>
<td>Poly lactic acid scaffolds</td>
<td>Promoted neuronal growth66</td>
</tr>
<tr>
<td>Micellar nanocomplexes</td>
<td>Promoted neuronal growth110</td>
</tr>
<tr>
<td>Nanoporous surface</td>
<td>Promoted neuronal differentiation111</td>
</tr>
<tr>
<td>Fluorescent polymeric nanovehicles</td>
<td>Promoted neuronal modulation112</td>
</tr>
<tr>
<td>Electrospun poly(methyl methacrylate) nanofibers</td>
<td>Promoted Schwann cells guidance113</td>
</tr>
<tr>
<td>Nanofiber membrane</td>
<td>Promoted neural tissue reconstruction114</td>
</tr>
<tr>
<td>Nanowires</td>
<td>Promoted nerve regeneration115</td>
</tr>
<tr>
<td>Titanium dioxide nanoparticle</td>
<td>Promoted neuronal–glial interaction116</td>
</tr>
<tr>
<td>Microgroove electroactive composite film</td>
<td>Promoted neuronal guidance117</td>
</tr>
<tr>
<td>Tenascin-C mimetic peptide amphiphile nanofiber</td>
<td>Promoted neuronal growth118</td>
</tr>
<tr>
<td>Chitin and carbon nanotube</td>
<td>Promoted neuronal growth66</td>
</tr>
<tr>
<td>Solid lipid nanoparticles</td>
<td>Promoted neuronal protection118</td>
</tr>
<tr>
<td>Electrospun silica nanofiber</td>
<td>Promoted neuronal growth44</td>
</tr>
<tr>
<td>Peptide nanofibers</td>
<td>Promoted neuorgenesis119</td>
</tr>
<tr>
<td>Galantamine/chitosan complex nanoparticles</td>
<td>Promoted neuronal protection20</td>
</tr>
<tr>
<td>Hybrid microfluidic system</td>
<td>Promoted neuronal differentiation21</td>
</tr>
<tr>
<td>Multiwalled carbon nanotubes</td>
<td>Promoted neuroprotection45</td>
</tr>
<tr>
<td>Carbon nanomaterials</td>
<td>Promoted neuronal adhesion46</td>
</tr>
<tr>
<td>Cationic nanoemulsion</td>
<td>Prevented neuroinflammation22</td>
</tr>
<tr>
<td>Nanofiber hydrogels</td>
<td>Promoted nerve regeneration93</td>
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</tbody>
</table>

inhibited neuronal differentiation.95 It was found that cerium oxide caused a decrease in neuron-specific β3-tubulin expression, a marker of neuronal differentiation, and glial fibrillary acidic protein, a neuroglial marker.91 In contrast to this report, cerium oxide nanoparticles promoted neurogenesis and abrogated hypoxia-induced memory impairment through AMP-activated protein kinase–protein kinase C–cAMP-response element binding protein (CREB)-binding protein signaling cascade in the rat.92 In another study, nanoparticle exposure did not impair cell viability and neuroinflammation in primary hippocampal cultures, but significantly decreased the neuronal differentiation markers in human SH-SYS5 cells.93 We do not know the reason of the contradicting responses of cerium oxide on neuronal cells, and the possibility of using different concentrations or different sizes of cerium oxide could be one of the reasons. Nevertheless, detailed studies must be undertaken with different sizes of cerium oxide to understand cerium oxide’s role.

Polyamidoamine (PAMAM) dendrimer has many biologic applications that include delivering gene or drug molecules to the cells. Despite having potential therapeutic and diagnostic application, PAMAM also caused some cytotoxic effects. It was reported that PAMAM dendrimer exposure caused an adverse effect on neuronal cell differentiation and adverse effect associated with oxidative stress and DNA damage.94 In addition, PAMAM dendrimer was reported to inhibit neurosphere growth. In the same study, it was reported that PAMAM reduced number of microtubule-associated protein 2-positive cells after 10 days of differentiation.94 In another report, AgNPs induced inflammatory response in neuronal cells.9 It was reported that AgNPs entered the nuclei of mouse neuronal cells and induced progression of neurodegenerative disorder.9 It was reported that silver nitrate treatment increased cellular superoxide dismutase activity and decreased mitochondrial membrane potential, leading to neuronal death.11 In addition, even a low concentration of AgNPs interrupted early neuronal processes and facilitated neuron apoptosis by increased cellular oxidative stress and mitochondrial disruption.11 In another study, it was reported that silica-indocyanine green/poly (ε-caprolactone) nanoparticles caused no neuronal differentiation because of mitochondrial damage.95 We have summarized other nanoparticles that are having inhibitory and cytotoxic effects on neurons, in tabular forms. For example, inhibitory and cytotoxic effects on neurons studied in in vitro models are shown in Table 2, whereas inhibitory and cytotoxic effects studied in animal models are shown in Table 3.

**Risks and challenges of nanoparticles on neuronal cells**

Despite having so many beneficial properties, the nanoparticles also cause some health concerns because of their small size and chemical compositions. Researchers were
interested to find out whether nanoparticles do exert some negative effects on the neuron biology. Recently, it has been reported that the use of low concentration of AgNPs caused neuronal damage and also treatment of silica nanoparticles impaired the mitochondrial function during neuronal differentiation. In another study, it was reported that PAMAM dendrimers with various surface functional groups caused cytotoxic effects on neuronal differentiation in human neural progenitor cells. These nanoparticles upon testing under in vitro conditions promoted neuronal damage and induced neurodegeneration, neuronal cytotoxicity, and neurotoxicity. Like in vitro models, nanoparticles have also been tested in animal models, which induced neuronal damage, neuronal degeneration, neuronal damage, neuronal toxicity, cell death, and impaired BBB. We have listed other nanoparticles that are also reported to cause toxic effects on neuronal cells, in Tables 2 and 3.

**Summary**

Nanoparticles have many potential applications, which include the promotion and activation of neuronal cell differentiation as reported in both in vitro and in vivo models. Nanoparticles can also reverse the neurologic impairments in the animal models of neurologic disorders such as brain ischemia and Parkinson’s and Alzheimer’s diseases. Research has shown that many nanoparticles promoted neuronal differentiation and enhanced neuronal survival and neuronal growth and maturation. But there are few nanoparticles that do not promote neuronal differentiation and cause neuronal damage or neurotoxicity. To achieve better response on the neuronal cells, researchers have used different sizes and shapes of nanoparticles. Sometimes one nanoparticle is conjugated with another nanoparticle or biomolecules to enhance the effects. Nanoparticles not only induce neuronal differentiation but also induce functional or behavioral recovery in animal models. The size of nanoparticles is also an important factor for their actions on the neurons. The researchers must know the size of nanoparticles before testing them for anticipated response. Most of the current data are based on morphologic, anatomical, and behavioral parameters, and still we do not know molecular mechanisms behind nanoparticle action on neurons. It would be interesting to study the molecular mechanism of the nanoparticle action on neurons.

**Table 2** List of various nanoparticles with neurotoxic effects on neurons tested in in vitro conditions

<table>
<thead>
<tr>
<th>Name of nanoparticles</th>
<th>Activities measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver nanoparticles</td>
<td>Promoted neuronal damage&lt;sup&gt;116&lt;/sup&gt;</td>
</tr>
<tr>
<td>Trimethyltin</td>
<td>Induced neuronal degeneration&lt;sup&gt;125&lt;/sup&gt;</td>
</tr>
<tr>
<td>Copper oxide nanoparticles</td>
<td>Induced neurodegeneration&lt;sup&gt;126&lt;/sup&gt;</td>
</tr>
<tr>
<td>Magnetite nanoparticles</td>
<td>Induced neuronal cytotoxicity&lt;sup&gt;127&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nanocrystals containing phospholipid micelles</td>
<td>Induced neurotoxicity&lt;sup&gt;129&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Table 3** List of nanoparticles with inhibitory effects on neurons, which are tested in animal models

<table>
<thead>
<tr>
<th>Name of nanoparticles</th>
<th>Activities measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trimethyltin</td>
<td>Induced neuronal degeneration&lt;sup&gt;125&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cadmium telluride</td>
<td>Induced neuronal damage and function&lt;sup&gt;126&lt;/sup&gt;</td>
</tr>
<tr>
<td>Carbon nanotubes</td>
<td>Induced neuronal toxicity&lt;sup&gt;126&lt;/sup&gt;</td>
</tr>
<tr>
<td>Nanofiber</td>
<td>Impaired blood–brain barrier&lt;sup&gt;124&lt;/sup&gt;</td>
</tr>
<tr>
<td>Graphene</td>
<td>Induced neuronal damage&lt;sup&gt;123&lt;/sup&gt;</td>
</tr>
<tr>
<td>Airborne nanoparticle</td>
<td>Induced cell death&lt;sup&gt;130&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Future direction
The nanoparticles hold a great promise for both diagnostic and therapeutic applications for various neurodegenerative diseases. They are also viable candidates to deliver neuroprotective molecules in the body for both diagnostic and therapeutic applications. The success of nanoparticles in neural areas depends on the consistent data generation, which depicts less variability in both in vitro and in vivo models. The cytotoxic effects of nanoparticles also need to be properly studied with proper dosages and correct treatment modalities to minimize the risk. Nanoparticles with stimulatory or inhibitory actions can be first studied through in vitro models, then through in vivo models. The results of both in vitro and in vivo studies must be compared and analyzed before calling nanoparticle stimulators or inhibitors. This strategy would help the researchers to identify and select potential nanoparticles for therapeutic and diagnostic purposes. Finally, nanoparticles with higher efficacy and ability to repair the damaged neurons with the least side effects in both in vitro and in vivo models hold great promise for the patients suffering from various neurodegenerative diseases.

Availability of data and material
The data analyzed are available from the corresponding author upon a request.

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Disclosure
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