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REVIEW

Impact of nanoparticles on neuron biology: current research trends

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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 different 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 modification[7–12] 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

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of nanoparticles is their precise targeting, biocompatibility, bioavailability, and multifunctional capabilities.[24–26] In the recent past, several attempts have been made to study the effect of different classes of nanoparticles on cancer cells.[27–38] 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.[3,39–43] To get better therapeutic results, various types of nanoparticles have been studied in neurons, and among those, carbon-based nanoparticles are mostly reported,[4,44–48] followed by gold and silver nanoparticles (AgNPs).[49–51]

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.[52–54] Furthermore, it has been reported that carbon nanotubes induced fibrogenesis on nanostructured substrates.[55] 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,[56] 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.[57] 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/Al_2O_3 nanoparticles showed disrupted BBB function and induced brain edema formation.[58] Moreover, AgNPs induced BBB destruction and astrocyte swelling and caused neuronal degeneration.[59] 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.[44,45,49,60–64] In addition, there are few reports about use of nanoscaffold,

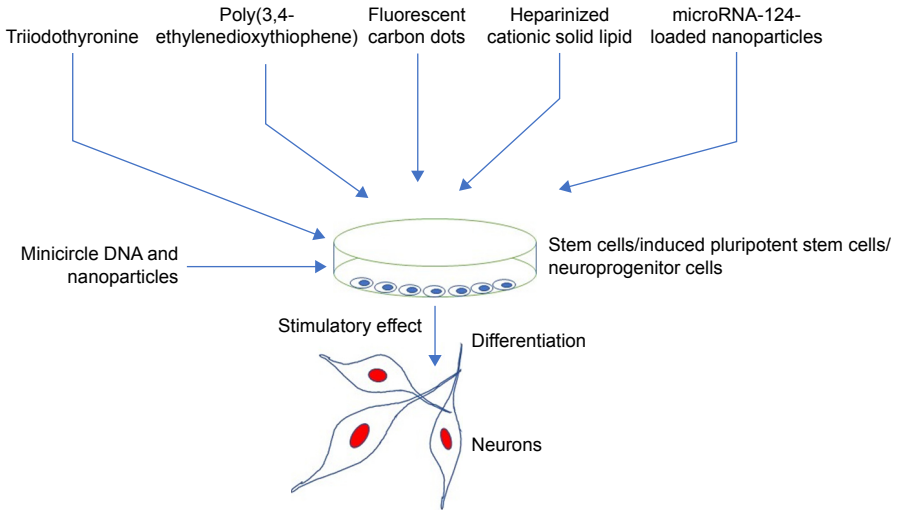

Figure 1 Stimulatory effect of nanoparticles on neuronal cells in an in vitro condition.

nanocomplexes, and nanomembrane in neuron regeneration and neural tissue reconstruction.[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.[68] For example, nerve growth factor (NGF)-encapsulated chitosan nanoparticles with size 80–90 nM caused differentiation of canine mesenchymal stem cells into neurons,[69] whereas calcium phosphate–lipid nanoparticles with size 30 nM caused neuronal differentiation.[70] In another report, it has been found that prodrug nanoparticles with 50 nM size improved neuronal survival.[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.[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.[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.[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.[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.[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.[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.[77] In addition, presence of neuron-specific staining in differentiated neuronal cells confirmed that NGF-loaded HCSLNs caused neuronal cell differentiation.[77] Recently, it was reported that traceable microRNA-124 -loaded nanoparticles, efficiently delivered into neural stem or progenitor cells, promoted neuronal differentiation and maturation.[78] 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.[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.[80] In another report, it was demonstrated that polyvinylidene fluoride and poly vinylidenefluoride-co-trifluoroethylene or BaTiO3

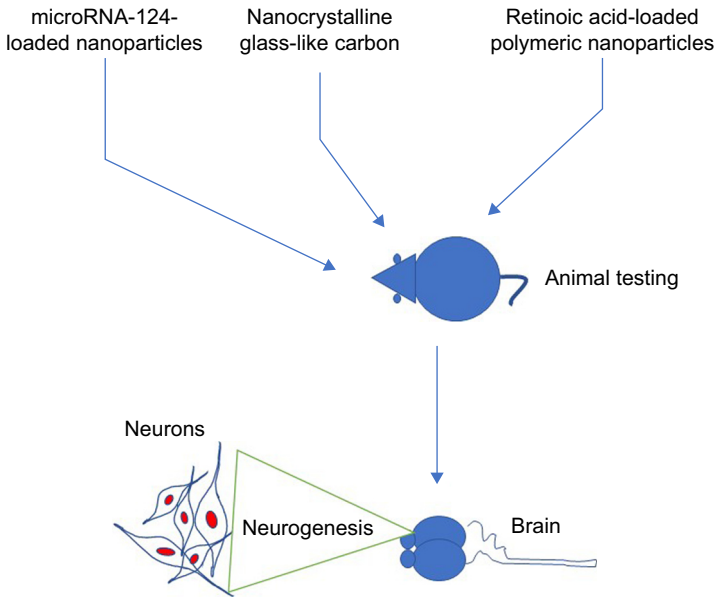

Figure 2 Stimulatory effect of nanoparticles on neuronal cell tested in animal models.

(barium titanate) stimulated and promoted differentiation of SH-SY5Y neuroblastoma cells.[81]

Nanotopography is also an important factor in neuronal differentiation. For example, nanostructured zirconia surfaces produced by supersonic cluster beam deposition of zirconia nanoparticles promoted neuronal differentiation and maturation of the hippocampus neurons.[82] Neurogenic niches constitute a powerful endogenous source of formation of new neurons to repair brain cells. Furthermore, it was reported that retinoic acid nanoparticles (RA-NPs) caused neurogenesis in the neural stem cells when the stem cells were exposed to blue light.[83] Application of nanoparticle extracellular matrix along with conductive fiber film promoted neurite adhesion, neural alignment, and elongation of neuritis.[84] The NGF-conjugated mesoporous silica nanoparticle was reported to promote neuron proliferation and neurite growth in pheochromocytoma (PC12) cell line.[85] In the same study, it was reported that use of NGF-conjugated mesoporous silica nanoparticle significantly promoted differentiation of neuron-like PC12 cells and growth of neurites compared to NGF alone.[85] This report suggests that use of nanoparticles along with NGFs improves neuronal cell differentiation many fold. Nanopatterned SU-8 surface using nanosphere lithography was reported to enhance neuronal cell growth.[86] Moreover, nanotopography also promoted neuronal differentiation of human iPSCs.[87]

The treatment of nanoparticles not only induces neuronal differentiation but also improves functional or behavioral recovery in animal models (Figure 2). For example, Zhang et al reported that treatment of small interfering RNA along with retinoic acid resulted in attenuation of neuronal loss and restoration of memory deficiencies in mice. Moreover, an intracerebroventricular injection of microRNA-124-loaded nanoparticles into a mouse model of Parkinson's disease caused an increased formation of new neurons in the olfactory bulb.[88] In the same study, it was found that microRNA-124-loaded nanoparticles enhanced migration of new neurons into the lesioned striatum of mice and caused improvement of motor function.[88] In another study, it was reported that an 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.[89]

In another report, it was demonstrated that RA-NPs enhanced vascular regulation of neural stem cell and promoted neuronal cell survival and neuronal cell differentiation after ischemia effect.[90] In addition, it was found that treatment of RA-NP protected endothelial cells from ischemic death and stimulated the release of prosurvival, proliferation-stimulating factors for neural stem cells.[90] It would be interesting to investigate the effect of triiodothyronine or microRNA-124-loaded nanoparticles in other animal models to check whether it can also enhance functional and behavioral recovery. In addition to use of nanoparticles for the neuronal differentiation, nanoparticles have also been used to deliver drugs in the neuronal cells. For example, it was reported that the minicircle DNA and nanoparticles were used to deliver a neurotherapeutic gene into neural stem cells.[80] In the same study, it was demonstrated that minicircles DNA along with magnetofection technology caused the overexpression of brain-derived neurotrophic factor gene in neural stem cells.[80]

We have summarized other nanoparticles based on their stimulatory actions in tabular form. For example, in Table 1, we have listed the nanoparticles with stimulatory effects on neurons tested under both in vitro culture 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.

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 and caused an inhibitory effect on the neural stem cells by inhibiting the neuronal cell differentiation.[91] In addition, detailed computational analyses showed that cerium oxide altered pathways and networks relevant to neuronal development and

Table 1 List of various nanoparticles with stimulatory effects on neurons

Name of nanoparticles	Activities measured
Nanofibrous scaffold	Promoted nerve regeneration[65]
Carbon nanotube	Promoted hippocampal neurons' activity[97]
Nanofibers	Promoted nerve regeneration[98]
Gold nanotubes	Promoted nerve regeneration[49]
Silica	Increased cell viability[99]
Gold nanocone	Increased neuronal growth[100]
BNDF-PS80-PBCA	Promoted neuronal differentiation[101]
Gatifloxacine	Promoted cerebral neuronal induction[102]
NTS-polyplex nanoparticle	Promoted gene expression in nigral dopaminergic neurons[103]
Core–shell nanoparticles	Promoted nerve regeneration[104]
Poly(lactide-co-glycolide) nanoparticles	Promoted nerve regeneration[105]
Electrospun fiber scaffolds	Promoted neuronal growth[60]
Magnetic nanoparticles	Reversed Parkinson's syndrome[106]
Zero valent zinc nanoparticles	Promoted neuronal proliferation[107]
Curcumin–docosahexaenoic acid-loaded carriers	Promoted neuronal survival[42]
Graphene and carbon nanotube	Promoted neuronal biocompatibility[108]
Active microcarriers	Promoted neuronal differentiation[109]
Gelatin/nanoceria nanocomposite fibers	Promoted neuronal regeneration[61]
Poly lactic acid scaffolds	Promoted neuronal growth[66]
Micellar nanocomplexes	Promoted axonal guidance[110]
Nanoporous surface	Promoted neuronal differentiation[111]
Fluorescent polymeric nanovehicles	Promoted neuronal modulation[112]
Electrospun poly(methyl methacrylate) nanofibers	Promoted Schwann cells guidance[113]
Nanofiber membrane	Promoted neural tissue reconstruction[114]
Nanowires	Promoted nerve regeneration[115]
Titanium dioxide nanoparticle	Promoted neuronal–glial interaction[116]
Microgroove electroactive composite film	Promoted neuronal guidance[117]
Tenascin-C mimetic peptide amphiphile nanofiber	Promoted neuronal growth[63]
Chitin and carbon nanotube	Promoted neuronal growth[46]
Solid lipid nanoparticles	Promoted neuronal protection[118]
Electrospun silica nanofiber	Promoted neuronal growth[64]
Peptide nanofibers	Promoted neurogenesis[119]
Galantamine/chitosan complex nanoparticles	Promoted neuronal protection[120]
Hybrid microfluidic system	Promoted neuronal differentiation[121]
Multiwalled carbon nanotubes	Promoted neuroprotection[45]
Carbon nanomaterials	Promoted neuronal adhesion[44]
Cationic nanoemulsion	Prevented neuroinflammation[122]
Nanofiber hydrogels	Promoted nerve regeneration[43]

inhibited neuronal differentiation.[91] 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-SY5Y 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 neutrosphere 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

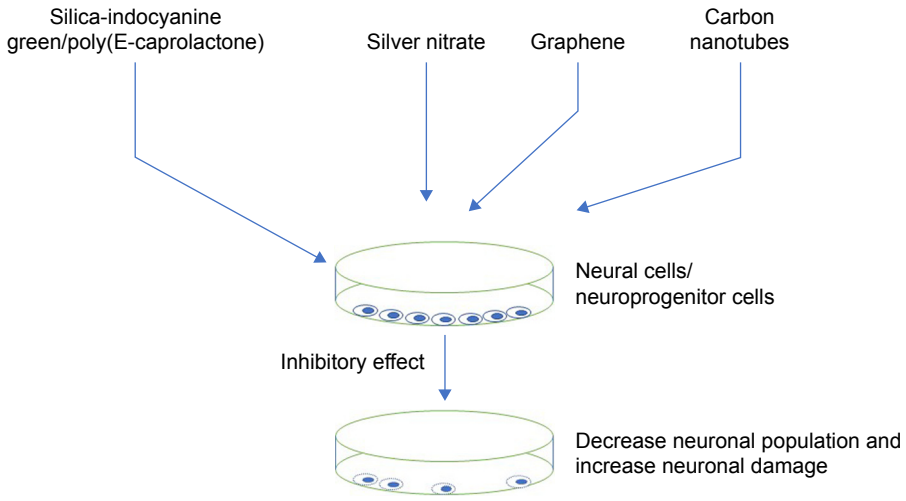

Figure 3 Inhibitory effect of nanoparticles on neuronal cells tested in an in vitro condition.

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[96] and also treatment of silica nanoparticles impaired the mitochondrial function during neuronal differentiation.[96] 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.[94] 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

Name of nanoparticles	Activities measured
Silver nanoparticles	Promoted neuronal damage[116]
Trimethyltin	Induced neuronal degeneration[125]
Copper oxide nanoparticles	Induced neurodegeneration[126]
Magnetite nanoparticles	Induced neuronal cytotoxicity[127]
Nanocrystals containing phospholipid micelles	Induced neurotoxicity[129]

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

Name of nanoparticles	Activities measured
Trimethyltin	Induced neuronal degeneration[125]
Cadmium telluride quantum dots	Induced neuronal damage and function[128]
Carbon nanotubes	Induced neuronal toxicity[48]
Nanofiber	Impaired blood–brain barrier[124]
Graphene	Induced neuronal damage[123]
Airborne nanoparticle	Induced cell death[130]

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

The authors report no conflicts of interest in this work.

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