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Nanometric agents in the service of neuroscience: Manipulation of neuronal growth and activity using nanoparticles

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Abstract

Nerve regeneration and recovery could provide great therapeutic benefits for individuals suffering from nerve damage post trauma or degenerative diseases. However, manipulation of nerves presents a huge challenge for neuroscientists and is not yet clinically feasible. In recent years, nanoparticles have emerged as novel effective agents for control of neuronal growth and behavior. Nanoparticles may facilitate the needed nerve manipulation abilities for therapeutic and diagnostic purposes including within the brain. This review aims at presenting the currently available literature regarding the interactions between inorganic nanoparticles and neurons. A wide range of nanoparticles are presented, including gold, silver, iron oxide, cerium oxide, nanotubes and quantum-dots. The nanoparticles enhance neuronal differentiation and survival, direct growth and regulate electrical activity. The studies are summarized in a concise table, arranged by the function and type of nanoparticle. The latest studies present a novel interdisciplinary approach, which could be harnessed for clinical applications in nanomedicine.

Key words: Nanoparticles; Neurons; Neuronal-growth; Neuronal-activity; Nanotechnology

Introduction

Nanoparticles are materials with a basic structural unit that has at least one dimension smaller than 100 nm in length. Due to their small size, nanoparticles can interact with and affect cells and tissues at the molecular level. In recent years, nanoparticles have emerged as a novel effective tool for manipulation of neuronal behavior, growth and differentiation.[1] Control of neuronal recovery could provide great therapeutic benefits for individuals suffering from nerve damage post trauma or degenerative diseases. In the US alone, 250,000-400,000 patients suffer from a spinal cord injury,[2] and 1.4 million sustain traumatic brain injury[3] each year. However, manipulation of nerve cells, which possess unique complex morphology and electrical activity, presents a huge challenge for neuroscientists, especially within the central nervous system, and is not yet clinically feasible. Nanoparticles may facilitate the needed nerve manipulation for therapeutic as well as diagnostic purposes.

Nanoparticles have different characteristics, i.e. the material they are made of, their size, shape, electric charge, magnetic and optical properties. Moreover, nanoparticles can be modified by conjugation of reactive functional groups and cargos. These characteristics determine the nature of the interactions between the nanoparticles and cells, such as the ability of nanoparticles to bind or penetrate into cells, or to affect biochemical reactions. The nature of the interactions determines the cellular response to the nanoparticles, as manifested by modifications of cellular morphology, activity or differentiation.

Nanoparticles can have cytotoxic effects,[4,5] likely because they induce the formation of reactive oxygen species that cause oxidative stress.[6,7] It is important to note, however, that there are substantial difficulties in assessing the toxicity of nanomaterials when interacting with biosystems, due to the lack of clear characterization of the materials when challenged in biological studies.[8,9] In the case of cationic nanoparticles, cytotoxicity is further enhanced by their ability to induce nanoscale disruptions in the plasma membranes of cells.[10-15] Nanoparticle coatings can also have cytotoxic effects, e.g. polydimethylamine, a frequently used coating for nanoparticles in biomedical applications, was

Abbreviations: NGF, nerve growth factor; BDNF, brain derived neurotropic factor.

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Q1 Table 1

	Activity	Type of nanoparticle (average dry size in nm)	Functional coating	Use	Active or mediator?	Toxicity?	Ref(s)
t1.2	Differentiation and survival	Quantum dots (15-20)	Conjugated to NGF	Labeling NGF for intracellular tracking, understanding the process of differentiation	Mediator	No	40
t1.3		Iron oxide (11)		Enhance differentiation of PC12 cells	Active	Yes (at high concentration)	41
t1.4		Gold nanorods (48.6 × 13.8)	Coated with poly(4-styrenesulfonic acid) or SiO_2	Enhance differentiation of NG108-15 cells	Active	No	42
t1.5		Iron oxide (23)	Conjugated to NGF	Stabilize NGF and thereby enhance neuronal differentiation	Mediator	No	56
t1.6		Piezoelectric boron nitride nanotubes (200-600 × 50)		Convert mechanical stress to electrical stimuli to enhance differentiation of PC12 and SH-SY5Y cells	Mediator	No	57
t1.7		Gold (20)		Deliver electrical stimulation to enhance differentiation of PC12 cells	Mediator	No	62
t1.8		Silver (110)		Enhance differentiation of SH-SY5Y cells	Active	No	83
t1.9		Iron oxide (15)	Conjugated to basic fibroblast growth factor	Enhance outgrowth of nasal olfactory mucosa cells	Mediator	No	90
t1.10		Cerium oxide (2-5)		Enhance survival of rat spinal cord cells	Active	No	93
t1.11	Directing neuronal migration and growth	Iron oxide (73)		Apply magnetic tensile forces to cause SH-SY5Y and primary Schwann cell cultures to migrate toward predefined directions	Mediator	No	81
t1.12		Iron oxide (25)	Conjugated to NGF	Apply magnetic tensile forces to induce directed neurite sprout in PC12 cells	Mediator	No	82
t1.13	Electrical activity	Zinc oxide (20-80)		Enhance electrical excitability of hippocampal neurons	Active	No	94
t1.14		Gold (5/40)		Enhance electrical excitability of neurons	Active	No	95
t1.15		Manganese ferrite (6)		Induce electrical activity in cultured neurons expressing a temperature sensitive ion channel, via radio frequency magnetic field heating	Mediator	No	102
t1.16		Carbon nanotubes (film of 50-70)		Enhance electrical excitability of neurons	Active	No	103
t1.17		Copper oxide (10-70)		Inhibit electrical excitability of hippocampal neurons	Active	No	96
t1.18		Silver (5, 50-100)		Inhibit electrical excitability of neurons	Active	No	98,99
t1.19		Carbon black (55)		Inhibit electrical excitability of primary murine cortical networks of neurons and glia cells	Active	No	100
t1.20		Iron oxide (<100)		Inhibit electrical excitability of primary murine cortical networks of neurons and glia cells	Active	No	100
t1.21		Titanium oxide (<100)		Inhibit electrical excitability of primary murine cortical networks of neurons and glia cells	Active	Yes (generate reactive oxygen species)	100
t1.22	Blood brain barrier	Gold (30)	Conjugated to insulin	Cross the blood brain barrier, can be detected by CT	Active (CT target) and mediator (carrier of ligand for crossing the blood brain barrier)	No	109
t1.23	Imaging and theranostics	Gold (50)		Single cell resolution CT imaging of glioma tumors in rats	Active	No	119
t1.24		Iron oxide (15)	Conjugated to a fluorescent dye and an antibody against amyloid-β peptides	Inhibit in-vitro amyloid aggregate formation in PC12 cells. Dye can be detected by MRI	Mediator	No	121
t1.25		Quantum dots (15-20)	Conjugated to BDNF or NGF	Intracellular tracking of single molecules	Mediator	No	126-128