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Review

Nanomaterial applications for neurological diseases and central nervous system injury

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ABSTRACT

The effectiveness of noninvasive treatment for neurological disease is generally limited by the poor entry of therapeutic agents into the central nervous system (CNS). Most CNS drugs cannot permeate into the brain parenchyma because of the blood-brain barrier thus, overcoming this problem has become one of the most significant challenges in the development of neurological therapeutics. Nanotechnology has emerged as an innovative alternative for treating neurological diseases. In fact, rapid advances in nanotechnology have provided promising solutions to this challenge. This review highlights the applications of nanomaterials in the developing neurological field and discusses the evidence for their efficacies.

Contents

Abbreviations: CNS, central nervous system; AD, Alzheimer's disease; PD, Parkinson's disease; SCI, spinal cord injury; BBB, blood-brain barrier; NPs, nanoparticles; FDA, food and drug administration; RES, reticuloendothelial system; PEG, polyethylene glycol; PLGA, poly(lactic-co-glycolic acid); PAMAM, polyamidoamine; PPI, polypropylenimine; PLA, poly(lactic acid); CNTs, Carbone nanotubes; QDs, Quantum dots; AuNPs, Gold nanoparticles; CT, computer tomography; MNPs, magnetic NPs; MPIOs, Magnetic iron oxide nanoparticles; SPIONs, superparamagnetic iron oxide nanoparticles; USPIONs, ultra-small superparamagnetic iron oxide nanoparticles; Aβ peptide, β-amyloid peptide; PCR, polymerase chain reaction; SAP, serum amyloid P; PBCA, poly(*n*-butyl cyanoacrylate); ApoE, apolipoprotein E; GONPs, graphene oxide nanoplatelets; MESFET, metal semiconductor field-effect transistor; SWCNTs, single-walled CNTs; NLPs, nanoliposomes; PA, peptide amphiphile; NAP, Novel active peptide; IndOH-LNCs, indomethacin-loaded lipid-core nanocapsules; DA, dopamine; AgNPs, silver NPs; UA, uric acid; AA, ascorbic acid; SLNs, solid lipid NPs; GNLs, gelatin nanostructured lipid carriers; GDNF, glial cell line-derived neurotrophic factor; Lf-PAMAM-NPs, lactoferrin-modified PAMAM NPs; i.v., intravenous; BMM, bone marrow macrophages; HTT, Huntingtin; MSCs, mesenchymal stem cells; C-SLNs, curcumin encapsulated SLNs; rt-PA, recombinant tissue plasminogen activator; MRI, magnetic resonance imaging; mCT, microCT; ELIP, echogenic liposome; BVP, Breviscapine; BVP-PLA-NPs, BVP-loaded poly (D, L-lactic acid) nanoparticles; CED, conversion enhancement delivery; P-gp, P-glycoprotein; MMPs, Matrix-degrading metalloproteises; HMGB1, high mobility group box 1; G4-SNAP, S-nitroso-*N*-acetylpenicillamine-derivatized generation-4 polyamidoamine; PARP-1, poly(ADP-ribose) polymerase-1; SOD-NPs, poly(D,L-lactide co-glycolide) NPs; MSCs, Bone marrow stromal cells; ESCs, embryonic stem cells; BSCB, blood spinal cord barrier; i.a., intra-arterial; PGA, polyglycolic acid; MP, methylprednisolone; PEO-PPO-PEO, poly(ethylene oxide)-b-poly (propylene oxide)-b-poly(ethylene oxide); CAP, compound action potential; TiO2, titanium dioxide; PCL, poly(ε-caprolactone); Gd, Gadolinium; US-Gd2O3, Ultra-small crystals of gadolinium oxide; CTX, chlorotoxin; PET, positron emission tomography; 5-ALA, 5-aminolevulinic acid; ICG, indocyanine green; FLS, fluorescein sodium; PAT, photoacoustic tomography; EGF, epidermal growth facto; HSP70, heat shock protein 70; Tf, transferrin; IVCLSM, intravital confocal laser scanning microscopy; TAM, tamoxifen.

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1. Introduction

Recent reports have shown that there are as many as 1.5 billion people worldwide suffering from central nervous system (CNS)-related diseases (Barchet and Amiji, 2009; Yang et al., 2010). CNS diseases, such as neurodegenerative diseases including stroke, SCI and brain tumors, are devastating and costly. The treatment of CNS diseases is currently inadequate because of the existence of the blood brain barrier (BBB) that tightly regulates the entry of foreign substances *e.g.*, a drug. In many cases, the amount of drug that enters the CNS is extremely limited and cannot seem to achieve an optimal beneficial effect without first affecting peripheral organs. Therefore, multiple strategies for drug delivery have been developed to enhance the delivery of therapeutic agents to the CNS.

Nanotechnology, an emerging treatment approach in medical science, is the manipulation of matter on a near-atomic size scale to produce new structures that have atomic, cellular or molecular functions. With their tiny dimensions, nanomaterials possess unique physiochemical properties such as conductivity, strength, durability and chemical reactivity, and are already being used in electronics, sunscreens, cosmetics, and medicines (Yoshioka et al., 2010). The advent of nanomaterials has also provided extraordinary opportunities for biomedical applications. The application of nanotechnology in the context of medicine is termed *nanomedicine* (Teli et al., 2010). Over the past decades, scientists have investigated the use of nanomaterials in the fields of drug delivery, targeted therapy and imaging to facilitate the development of treating CNS-related diseases. Furthermore, nanomaterials are inert, which make them stable and allow binding to specific ligands thereby enhancing their use for targeted therapy (Mouhieddine et al., 2015). Herein, by summarizing the diversity of nanomaterials in current use, we aim to introduce the advances of nanomaterial development and provide a basic understanding of nanotechnology applications in CNS-related diseases.

2. General information on the various types of nanomaterials

To date, many types of nanomaterials including Liposomes, Micelles, Polymeric Nanoparticles (NPs), Carbon Nanotubes, Quantum Dots and Metallic NPs, have been fabricated and used to treat neurological disorders as Fig. 1 shows (Srikanth and Kessler, 2012).

2.1. Liposomes

Liposomes are uni- or multi-lamellar lipid bilayers composed of amphipathic phospholipids. They consist primarily of phosphatidylcholine (lecithin) and surround an aqueous compartment. The Food and Drug Administration (FDA) approved methods for producing liposomes include sonication, extrusion, reverse-phase evaporation and solvent injection (Johnston et al., 2008). Liposomes can be classified as cationic, anionic or neutral, based on their overall net charge (Sharma et al., 2012), and they possess the ability to cross the BBB more easily than other compounds due to their lipophilic nature. Their main advantages include host tolerance and high degradability with less toxic effects. Although liposomes have the advantage of being able to be loaded with more drugs, their easy degradation by the reticuloendothelial system (RES) is a notable disadvantage. As such, a reduction in the particle size ($<$100 nm) or modification with polyethylene glycol (PEG) gives them a stealth-like property to overcome their rapid degradation (Nair et al., 2012).

2.2. Micelles

Micelles are formed when amphiphiles are placed in an aqueous medium. Upon contact, the nonpolar water environment pushes the nonpolar portions of amphiphiles into the interior part to form a hydrophobic core, which acts to store poorly water-soluble drugs. On the other hand, the polar portions are forced onto the exterior surface to form a hydrophilic shell, which can protect