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Size, surface charge, and shape determine therapeutic effects of nanoparticles on brain and retinal diseases

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Abstract

Nanoparticles can be valuable therapeutic options to overcome physical barriers to reach central nervous system. Systemically administered nanoparticles can pass through blood-neural barriers; whereas, locally injected nanoparticles directly reach neuronal and perineuronal cells. In this review, we highlight the importance of size, surface charge, and shape of nanoparticles in determining therapeutic effects on brain and retinal diseases. These features affect overall processes of delivery of nanoparticles: *in vivo* stability in blood and other body fluids, clearance via mononuclear phagocyte system, attachment with target cells, and penetration into target cells. Furthermore, they are also determinants of nano-bio interfaces: they determine corona formation with proteins in body fluids. Taken together, we emphasize the importance of considerations on characteristics of nanoparticles more suitable for the treatment of brain and retinal diseases in the development of nanoparticle-based therapeutics.

From the Clinical Editor: The central nervous system (CNS) remains an area where drug access and delivery are difficult clinically due to the blood brain barrier. With advances in nanotechnology, many researchers have designed and produced nanoparticle-based systems in an attempt to solve this problem. In this concise review, the authors described the current status of drug delivery to the CNS, based on particle size and shape. This article should stimulate more research to be done on future drug design.

Key words: Nanoparticles; CNS disease; Drug delivery systems; Nanoparticle design; Blood-neural barriers

Nanoparticles as novel therapeutics for human diseases

Nanoparticles have several advantages as therapeutic materials for various human diseases including brain and retinal diseases. 1) They can pass through biological barriers, especially blood-neural barriers including blood–brain barrier (BBB) and blood-retinal barrier (BRB).[1] It is critical to develop modalities to enhance bioavailability in target organs, the brain and the retina, in the development of therapeutic agents for brain and retinal diseases.[2] 2) At the same time, as a novel drug delivery system, nanoparticles help therapeutic agents to stay longer in target organs. Generally, physicochemical properties of nanoparticles enhance bioavailability of therapeutic agents after both systemic and local administration.[3,4] 3) Furthermore, nanoparticles by themselves exert therapeutic actions. Cerium oxide nanoparticles (nanoceria) are known to induce anti-inflammatory effects.[5] Interestingly, inorganic nanoparticles such as gold, silver, and silica nanospheres also exhibit 'self-therapeutic' effects without surface modification.[6–9]

Then, which characteristics of nanoparticles make them attractive for therapeutic uses? First of all, nanoparticles are smaller than previously developed drug delivery systems such as microparticles and liposomes. Nanoparticles are defined as small particles of which three dimensions are nanoscale, one to few hundred nanometers.[10] The size of nanoparticles (less than 1 μm)

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enables penetration over biological barriers and extended bioavailability in tumor tissues.[1,11] 'Small' nanoparticles can pass through barriers even when they are intact. Therefore, they penetrate leaky tumor vessels more easily. The more attractive characteristic of nanoparticles is that we can control the properties of nanoparticles including size, shape, and surface characteristics. Addition of ligands or receptors onto the surface of nanoparticles enhances target-specificity.[12] Furthermore, various conditions and additives result in a diverse spectrum of nonspherical and spherical nanoparticles such as nanospheres, nanocubes, nanorods, nanocages, and platonic solids during colloid-chemical synthesis.[13,14] In addition, 'top-down' engineering techniques produce mono-disperse shape-specific nanoparticles with microfluidic systems or imprint lithography approaches.[15]

With these characteristics, well-designed nanoparticles enhance or suppress biological activity regarding pathological conditions. In particular, it is remarkable that most biological interactions occur among nano-sized molecules such as growth factors, cell surface receptors, intracellular organelles, and signaling molecules. Nanoparticles also interact with proteins in biological media,[16] inhibit biological activity of growth factors by binding with them as antibody does,[17] and utilize cell machinery including cell surface molecules and intracellular organelles.[18] Interestingly, physicochemical characteristics of nanoparticles can affect cellular uptake, biological distribution, penetration into biological barriers, and resultant therapeutic effects.[11,19] These features may be related with therapeutic effects on brain and retinal diseases in which blood-neural barriers act as an obstacle to therapeutic agents.

In this review, we focused on the therapeutic potential of nanoparticle-based therapeutics for brain and retinal diseases. Particularly, we discussed differential effects of size, surface characteristics, and shape of nanoparticles on biological activity. Shape, inter alia, has to receive more attention because relatively fewer studies were performed about it than the other factors (size and surface charge). In addition, we mentioned the complexity of nano-bio interface, the formation of 'corona' around nanoparticles, which is implicated in the biological activity of nanoparticles and affected by differential characteristics of nanoparticles as well. A schematic understanding of the roles of physicochemical properties of nanoparticles on therapeutic effects might help to design rationale-based nanoparticles for the treatment of brain and retinal diseases.

Nanoparticles and diseases of central nervous system (CNS)

Nanoparticles and brain diseases

As in other organs, malignant tumors are one of the most frequently studied target diseases of nanotherapeutics among brain diseases. In particular, various pathological mechanisms including reactive oxygen species (ROS), biological actions of growth factors, and signaling pathways of proliferative potentials could be addressed with nanoparticle-based therapeutics.[20,6] In addition, dual functions of nanoparticles in both imaging and therapy, so-called theranostics, are still attractive concepts.[21] A notable characteristic of nanoparticles is that it is possible to enhance bioavailability of therapeutic agents in brain tumors by conjugation of specific ligands onto the surface of nanoparticles which are loaded with therapeutic materials. BBB could be an obstacle to therapeutic agents as well as toxic materials.[22] Bioavailability can be enhanced by ligand modification with peptides targeting cell surface receptors which are abundant in endothelial cells lining brain vasculatures, such as transferrin receptor and low-density lipoprotein receptor.[23,24] Therapeutic materials including conventional chemotherapeutic agents and small interfering RNA can be loaded in nanoparticles. In addition, ligand modified nanoparticles enhance cellular uptake of therapeutic materials into malignant tumor cells by conjugation with ligands which bind to surface molecules specific to glioma cells.[25] Packing with two or more therapeutic materials into nanoparticles is also a plausible strategy in the treatment of brain tumor.[26]

Neurodegenerative diseases, such as Alzheimer's, Huntington's, and Parkinson's diseases, are also the targets of nanoparticle-based therapeutic approaches. Similarly to malignant tumors, overcoming BBB is one of the causes for the use of nanoparticles in the treatment of neurodegenerative diseases. Biomolecules including nerve growth factor (NGF), brain-derived neurotrophic factor, and thyrotropin-releasing hormone (TRH) exert neuroprotective effects, but are limited in the biological activity because they are rapidly metabolized in systemic circulation and cannot overcome BBB. Nanoparticle-based approaches open the opportunity for these molecules in the treatment of neurodegenerative diseases.[27–29] Intravenous administration of NGF-containing poly(butyl cyanoacrylate) nanoparticles coated with polysorbate 80 demonstrates the efficient transport of NGF across the BBB.[27] In this study, polysorbate 80 coating is a tool for targeting of therapeutic nanoparticles to brain.[30] In a study using biodegradable nanoparticles, anticonvulsant effects of TRH are observed with intranasal delivery of TRH-loaded polyactide nanoparticles even without surface modification with specific ligands.[29] Likewise, poly(lactic-co-glycolic) acid (PLGA) nanoparticles enhance brain delivery of nicotine, which provides neuroprotection against ROS-induced parkinsonism.[31] In addition, ligand modification with lactoferrin, of which receptor is highly expressed in neurons, can be a strategy to increase the concentrations of therapeutic agents in the brain.[32]

Ischemic injury in the brain might receive benefits from the development of adequate nanotherapeutics. Overcoming pathological events associated with reperfusion is the focus of the development of therapeutic agents for ischemic stroke. In this context, researches have been performed to improve the bioavailability of antioxidant molecules and to investigate the antioxidant effects of nanoparticles by themselves.[33–36] Dendrigraft poly-L-lysine nanoparticles conjugated with dermorphin, a μ-opiate receptor-specific heptapeptide, enhances the delivery of short hairpin RNA targeting apoptosis signal-regulating kinase 1, which is involved in oxidative stress, to the brain with intravenous administration.[33] Similarly, PLGA nanoparticles containing superoxide dismutase, one of antioxidants, also showed localization in the brain, reduced infarction volume, and improved behavior in mice with cerebral ischemia–reperfusion injury.[34] Another interesting part regarding therapeutic potential of nanoparticles is that they exert therapeutic actions by themselves without surface modification. 3 nm-sized platinum nanoparticles and nanoceria demonstrate protective