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PERSPECTIVE ARTICLE

Nanotherapies: A potent treatment for neurodegenerative diseases

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Abstract

It is generally reported that neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease, pose severe threats to global public health. Traditional therapies for neurodegenerative diseases exhibit low drug delivery efficiency due to the restrictive nature of the blood–brain barrier. Fortunately, nanomedicines can effectively overcome blood–brain barrier through mechanisms such as intercellular penetration and receptor targeting, which have advantages such as controlled release, reduced toxicity, and enhanced efficacy. In this paper, we summarize the latest research progress based on the types of nanomaterials, administration approach, and implications, with the aim of providing insights for optimizing the research and development of nanomedicines for neurodegenerative diseases.

Keywords: Nanotherapy; Neurodegenerative diseases; Drug delivery; Targeted delivery

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1. Background

Neurodegenerative diseases represent the most prevalent disorders affecting the central nervous system (CNS), with key examples including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease, frontotemporal dementia, and amyotrophic lateral sclerosis (ALS). These diseases cause problems related to movement disorders or mental functional disorders and greatly aggravate patients' quality of life.[1,2] Specifically, AD already impacts more than 55 million people globally, a number that has been projected to reach 78 million by 2030. Based on the 2019 estimates by the World Health Organization, 850,000 people are affected by PD worldwide.[3] Amid the accelerated global aging, populations worldwide face substantial burdens from the rising costs associated with neurodegenerative diseases.

Despite rapid advancements in medical technology, effective therapeutic strategies for most neurodegenerative diseases remain unavailable in clinical practice. For instance, donepezil, aducanumab, rivastigmine, memantine, and galantamine for AD, and *L*-3,4-dihydroxyphenylalanine (L-DOPA) for PD, merely delay disease progression, rather than providing a cure. Delivery of therapeutics to the CNS is limited by the blood–brain barrier (BBB; Figure 1), which acts like a two-edged sword: while it protects brain tissues, it further imposes restrictions on the access of a range of therapeutics into the CNS.[4] It is worth mentioning that almost all macromolecular drugs and over 98% of small-molecule drugs fail to traverse the BBB.[5] Hence, identifying effective approaches to cross the BBB are crucial for improving the delivery efficiency of therapeutics in neurodegenerative disease treatment.

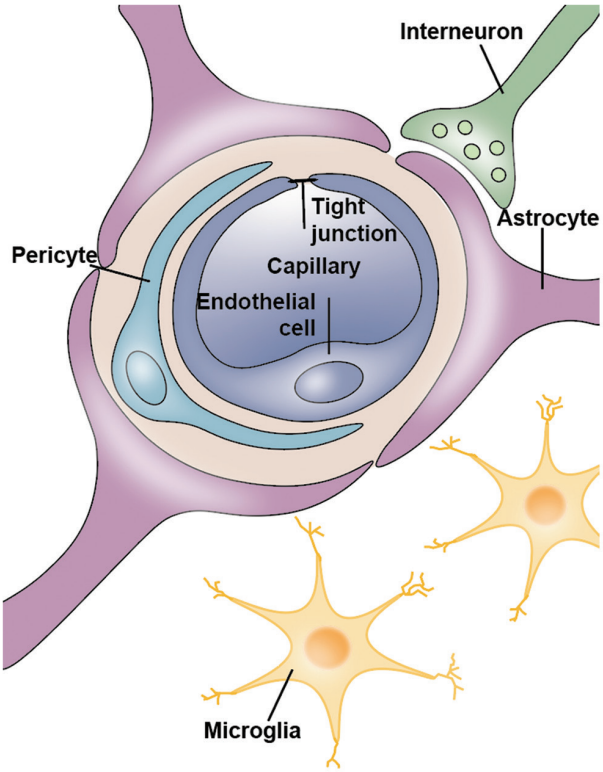

Figure 1. Schematic diagram of blood–brain barrier. Adapted from Cui *et al.*[6] with modifications.

Nanoparticles (NPs) emerge as a promising solution. With diameters varying from 1 nm to 100 nm, NPs possess distinct advantages such as the ability to encapsulate drugs, enable minimal dosage requirements, enhance drug stability, achieve controlled or sustained release, and reduce toxic side effects.[7-9] Most importantly, through intercellular penetration and receptor targeting effects, NPs can traverse the BBB. More precisely, NPs with sufficiently small particle sizes can utilize the intercellular spaces between tight junctions for intercellular penetration.[10] Receptor targeting is achieved by attaching specific ligands to NPs' surfaces, enabling receptor-mediated endocytosis of the NPs. Subsequently, the NPs undergo transcytosis across endothelial cells, allowing them to traverse the BBB.[8] Given these unique features, nano-delivery systems facilitate drug delivery across the BBB and enhance CNS targeting efficiency, offering new prospects for neurodegenerative diseases.[4] Until now, various nano-systems have been applied in neurodegenerative diseases, including solid lipid NPs (SLNPs), liposomes, gold NP, non-polymeric micelles, dendrimers, lipoplex, polymeric micelle, nanotubes, polymeric NP, quantum dots, and magnetic NP (Figure 2).[9]

At the forefront of nanotechnology development, this perspective aims to summarize the current status of

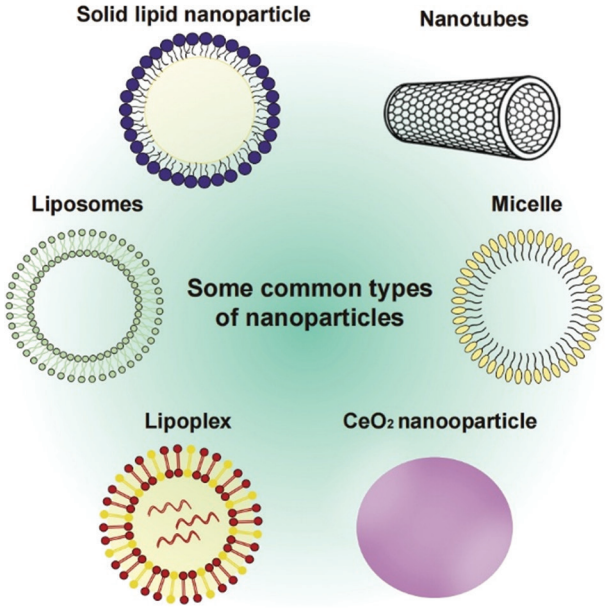

Figure 2. Some common types of nanoparticles. Adapted from Akhtar *et al.*[9] with modifications.

the field. For a better, logical presentation, we focus on three dimensions: types of nanomaterials, administration routes, and their implications, highlighting recent research progress and offering insights into addressing key challenges in the use of NPs for neurodegenerative disease treatment.

2. Classification by nanomaterials

Currently, various nanomaterials are used to treat neurodegenerative diseases, each with unique merits in drug delivery and efficacy by virtue of their structural differences.

Lipid-based nanocarriers mainly include liposomes and SLNPs.[11] Liposomes are spherical structures made up of one or more bilayers, which consist of phospholipids of natural or synthetic origin.[12] Lipid-based nanocarriers are among the safest and most promising platforms for neurodegenerative disease therapy due to their biocompatibility, structural flexibility, and ability to deliver targeted compounds across the BBB while specifically homing to brain cells.[13] Recent research has demonstrated the potential of transferrin-modified liposomes linked to vitamin B12 as a therapeutic for AD. The formulation targets both neuronal cells and the BBB, effectively slowing the aggregation of amyloid-beta (Aβ) fibrils, demonstrating considerable promise for AD treatment.[11] Notably, SLNPs offer distinct advantages, including the capacity to traverse physiological barriers and enhance drug bioavailability without requiring high doses. These particles can direct

active compounds to intended targets, significantly reducing toxicity to surrounding tissues while protecting payloads from chemical and enzymatic degradation. Preclinical studies have shown that functionalized SLNPs loaded with nicotinamide can improve cognitive function in AD animal models by decreasing tau hyperphosphorylation. Furthermore, SLNPs encapsulating rivastigmine tartrate have been designed to enhance intranasal delivery into the brain for AD treatment.[11] In a nutshell, lipid-based nanocarrier systems have shown positive properties, including sustained drug release profiles, improved CNS bioavailability, and enhanced therapeutic efficacy.[14]

Polymeric NPs have been integrated into clinical practice for several decades, demonstrating their long-standing application potential.[7] These solid particles consist of organic colloidal NPs fabricated from polymeric, natural, or synthetic materials. There is no doubt that poly(D,L-lactide-co-glycolide) (PLGA) and chitosan are the most widely used in AD treatment.[11] PLGA NPs exhibit excellent biocompatibility and biodegradability, rendering them ideal for the regulated release of therapeutic molecules. These NPs are capable of encapsulating drugs or other therapeutics, and further support the targeted delivery of these payloads to the brain. Chitosan NPs, obtained from chitin, which is recognized for its favorable biocompatibility and low toxicity, have also been investigated for their application potential in AD therapy. Chitosan NPs are capable of encapsulating drugs or therapeutic agents, thereby enabling targeted drug delivery to specific sites.[8] However, polymer-based nanomedicines are not without limitations. Some polymers (like polyquaternium polymers) may cause toxicity or inflammation, raising regulatory concerns.[15]

3. Categorization by administration approach

The administration route of NPs is key to determining their biodistribution patterns, brain deposition, and influences the effectiveness of nanotherapeutic interventions.

For the treatment of neurodegenerative diseases, oral administration is widely recognized as a preferred route due to its safety, high patient adherence, and convenience. Nevertheless, a major challenge persists: many therapeutic agents are prone to degradation in the gastrointestinal tract and have difficulty crossing the gastrointestinal mucosal barrier, which in turn leads to low systemic bioavailability.[16] A key concern for pharmaceutical researchers has long been identifying strategies to preserve drug stability while boosting drug absorption in the gastrointestinal environment. Multiple studies have confirmed that lipid NPs (LNPs) exhibit strong competence to encapsulate diverse bioactive agents (including RNA, DNA, small-molecule drugs, and proteins) and protect them against enzymatic degradation in the body. Beyond protection, LNPs also facilitate drug transit across gastrointestinal physiological barriers through diverse transport mechanisms, significantly boosting the absorption of oral drugs. Furthermore, functionalizing LNP surfaces with specific targeting ligands enables precise delivery to diseased brain cells or tissues, making LNPs promising oral drug delivery systems for neurodegenerative disease.[17]

Injection is commonly used for targeting nanomedicines to the CNS, particularly in cases of neuroinflammation with impaired BBB.[18] The core merit of intravenous delivery is the rapid onset and complete bioavailability of drugs even with low doses, while avoiding first-pass metabolism. A study demonstrated that a single intravenous injection of reactive oxygen species-responsive NPs enabled targeted drug release within affected brain regions, concurrently activated autophagy, attenuated neuroinflammation, markedly reduced Aβ burden, and reversed cognitive deficits in a mouse model of AD.[19] However, this approach may induce systemic infections while showing weak efficacy in drug targeting.[18,19]

Compared with conventional oral or intravenous administration, intranasal administration boasts multiple advantages, including non-invasiveness, ease of administration, patient acceptability, and the competence to traverse the BBB for direct drug delivery into the CNS. These features make it a compelling choice compared to invasive approaches such as injection and oral therapy.[8,9] For instance, PLGA NPs loaded with lamotrigine attained higher brain concentrations and superior efficacy in animal models compared to oral delivery. In addition, advanced formulations including polyethylene glycol (PEG)-modified chitosan-lipid nanocapsules or carbon nanotubes have shown significant potential for nasal drug administration, further enhancing therapeutic results. When combined with nanotechnology and biomaterials, intranasal drug delivery technology offers a novel non-invasive therapeutic strategy for neurodegenerative diseases (and other fields), highlighting substantial potential for clinical application.[20]

4. Categorization by implication

Owing to the complexity of brain function, treating neurodegenerative diseases has long posed a major challenge. Nevertheless, owing to the ongoing rapid advancements in the fields of nanomaterials and nanotechnology, these nanoscale materials are expected to offer long-term therapeutic hope.

As one of the most prevalent neurodegenerative diseases, AD is a progressive and irreversible nervous

system disorder. Currently, no effective therapeutic approaches exist to alleviate symptoms of AD or achieve a cure.[6] Inhibiting or blocking the pathogenic mechanism by NPs is a key strategy to treating AD.[21] For instance, gold NPs (AuNPs) functionalized by tryptophan-proline-methionine can alleviate oxidative stress, as well as regulate behavior and the cholinergic system, thereby enhancing neuroprotective efficacy in AD model mice.[22] Guo *et al.*[23] illustrated that multifunctional selenium quantum dots not only effectively inhibited Aβ aggregation but also alleviated oxidative stress and restored mitochondrial function. In addition, Yang *et al.*[24] showed that fucoxanthin-loaded PLGA-PEG NPs penetrate the BBB and release fucoxanthin in a sustained manner, preventing cognitive impairment in AD model mice induced by Aβ with higher efficacy than free fucoxanthin.[25] These results indicate that NPs may serve as a suitable therapeutic strategy against AD. Nonetheless, critical issues such as the *in vivo* metabolism of metal ions and their potential toxicity require consideration.[19]

PD is characterized by abnormal basal ganglia function, which leads to the aberrant build-up of Lewy bodies within the substantia nigra and the decrease of dopaminergic neuronal populations.[26] Currently, levodopa preparations serve as the primary therapy for PD, but they provide only modest symptom relief, do not halt disease progression, lack long-term efficacy, and are associated with a high incidence of side effects.[6,19] NPs have shown promise in overcoming these limitations: Mn_3O_4 NPs effectively lowered α-syn levels in the cerebrospinal fluid of PD model mice, enhanced the cognitive abilities, and showed favorable biodegradability. AuNPs counteracted PD symptoms caused by reserpine in C57BL/6 mice and reduced reserpine-induced neuronal apoptosis. These results highlight NPs' potential as a promising therapeutic option for PD.[19]

In addition, advanced nanotherapeutic attempts for Huntington's disease include nanotechnology-optimized adeno-associated virus vector-mediated gene editing. In the treatment for ALS, lactoferrin-modified LNPs facilitated the transport of riluzole across the BBB through interaction with lactoferrin receptors expressed on brain endothelial cells.[27]

However, research on some neurodegenerative diseases remains scarce, such as progressive supranuclear palsy and spinocerebellar ataxia. We are anticipating to see the related research in the near future.

5. Conclusion and indication

Nanotherapy, as an innovative strategy to overcome the treatment challenges of neurodegenerative diseases, has been extensively validated for its ability to bypass the limitations of traditional drug delivery while enhancing the accuracy and safety of therapies.[28] Particularly, it has shown remarkable potential in the treatment of diseases such as AD and PD.[7]

Based on the research progress discussed above, this perspective outlines the implications for the development of nanomedicines as follows. First, the biocompatibility of nanomaterials and the safety of encapsulated drugs are the core prerequisites for clinical transformation, in which case it is necessary to assess the stability of long-term efficacy and safety of NPs.[29] Second, studies have confirmed that non-invasive approaches, such as intranasal administration, offer advantages including the ability to cross the BBB.[4,30] Thus, the process of their translation from fundamental research to clinical practice should be accelerated. On the other hand, the feasibility of emerging approaches such as transdermal and inhalation administration should be explored to build a diversified administration system. Third, current nanotherapy research primarily targets high-incidence neurodegenerative diseases, while rare and orphan conditions receive comparatively little attention. Moving forward, it is necessary to strengthen research on these conditions and broaden the application of nanomedicines to more neurodegenerative diseases.

With continuous innovation and the resolution of current challenges, NPs have the potential to revolutionize the treatment field of neurodegenerative diseases in the coming decades.[30] We look forward to the successful introduction of safe and effective nanomedicine products in the near future, offering new therapeutic hope to patients worldwide.

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Conflict of interest

The authors declare they have no competing interests.

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Ethics approval and consent to participate

Not applicable.

Consent for publication

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