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Review Article

Advances in nanotechnology for targeted drug delivery in neurodegenerative diseases

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Abstract: Neurodegenerative diseases, including Alzheimer's, Parkinson's, and multiple sclerosis, are a growing healthcare challenge due to their impact on quality of life and the difficulty in treating them. These disorders are associated with brain lesions and barriers, such as the blood-brain barrier (BBB), that impede effective treatment. Nanotechnology, especially functionalized nanoparticles (NPs), is emerging as a promising tool for overcoming these barriers. Nanoparticles, such as liposomes, polymeric micelles, and gold nanoparticles (AuNPs), show potential for targeted drug and gene delivery to the brain, enhancing bioavailability, circulation time, and treatment efficacy. Nanocarrier-based systems have demonstrated success in protecting nucleic acids from degradation, improving BBB penetration, and delivering genetic material to target specific brain areas. Exosomes and artificial vesicles also hold promise for their size and biocompatibility. Gold nanoparticles are gaining attention for their neuroprotective and anti-inflammatory properties, particularly in treating Alzheimer's, Parkinson's, and stroke. These systems can modify gene expression and address the underlying mechanisms of these diseases. In addition to drug delivery, noninvasive strategies like intranasal administration are being explored to enhance patient adherence. However, challenges remain, including regulatory hurdles and the need for further research to optimize these technologies. As research advances, the synergy between materials science, bioengineering, and medicine will pave the way for more effective treatments for neurodegenerative diseases. The aim of this study is to explore the potential of functionalized NPs in overcoming the BBB and improving targeted drug delivery for the treatment of neurodegenerative diseases.

Keywords: Exosomes, polymeric nanoparticles, neurodegeneration, therapeutic potential, neurodegenerative disorders, nanotechnology

Introduction

Neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's diseases, present major challenges due to the progressive loss of neurons and the lack of effective treatments [1]. One of the primary obstacles in treating these conditions is the blood-brain barrier (BBB), which prevents most therapeutic agents from reaching the brain. As a result, drug delivery to the central nervous system (CNS) remains a significant hurdle [2].

Recent advancements in drug delivery systems, particularly in nanotechnology and biologically derived vesicles, are offering new ways to overcome the BBB [3]. These systems, including lipid-based nanoparticles, polymeric micelles, and extracellular vesicles, enhance drug stability, bioavailability, and targeted delivery to the brain. By improving the precision and effectiveness of treatment delivery, these technologies have the potential to revolutionize the treatment of neurodegenerative diseases [4].

Nanotechnology-based drug delivery systems employ several mechanisms to cross the BBB and deliver therapeutic agents to the brain. One primary method is receptor-mediated transcytosis (RMT), where nanoparticles are functionalized with ligands that bind to specific receptors on endothelial cells of the BBB. This interaction facilitates the internalization and transport of the nanoparticles across the barri-

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er [5]. Another approach is adsorptive-mediated transcytosis (AMT), which utilizes positively charged nanoparticles to interact with negatively charged cell membranes, promoting nanoparticle uptake and transport. Furthermore, nanoparticles can be engineered to exploit endogenous transport pathways or temporarily disrupt the BBB to allow drug passage [6]. Lipid-based carriers, such as liposomes and polymeric micelles, mimic natural biological structures, improving biocompatibility and enhancing their ability to penetrate the BBB. Additionally, gold nanoparticles (AuNPs) are being investigated for their ability to cross the BBB due to their tunable size, surface properties, and potential neuroprotective effects [6, 7].

This review explores the cutting-edge drug delivery systems that show promise in treating CNS disorders, highlighting their mechanisms, challenges, and potential for clinical application. Recent advancements in drug delivery systems have made significant strides toward addressing the challenges posed by neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and other CNS disorders [7]. These diseases present unique challenges due to the complex and often resistant BBB, poor drug solubility, low bioavailability, and other issues that hinder the effectiveness of traditional therapies. In response, researchers have developed innovative, advanced drug delivery systems, which include lipid-based nanoparticles, nanoscale drug carriers, extracellular vesicles (EVs), and functionalized nanoparticles [4, 8]. These systems aim to enhance the stability, bioavailability, and targeted delivery of therapeutic agents, particularly those intended for the brain.

Methods

Study design

A comprehensive literature review was conducted to investigate nanotechnology-based drug delivery systems targeting neurodegenerative diseases. The study focused on various delivery mechanisms that cross the BBB and their potential applications in treating Alzheimer's, Parkinson's, and Huntington's diseases. This review was conducted in alignment with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure transparency and rigor in data collection and reporting.

Search strategy

A systematic search was performed across multiple databases, including PubMed, MEDLINE, Scopus, Web of Science, and Google Scholar, covering literature published between January 2015 and August 2024. The search terms used included '(nanoparticle OR nanotechnology) AND (blood-brain barrier OR BBB) AND (Alzheimer OR Parkinson OR Huntington OR neurodegenerative)'. Only peer-reviewed articles published in English were included to ensure scientific validity and accessibility.

The inclusion criteria were as follows: (1) studies focusing on nanotechnology-based drug delivery systems targeting neurodegenerative diseases, (2) articles describing mechanisms to cross the BBB, and (3) preclinical or clinical studies evaluating the efficacy and safety of these delivery systems. Exclusion criteria included: (1) studies unrelated to neurodegenerative conditions, (2) articles without experimental or clinical data, and (3) review articles without original research findings.

Additional relevant studies were identified by screening the references of previously published review articles. After applying the inclusion and exclusion criteria, a total of 9 research articles were selected for qualitative synthesis.

In the selected studies, the evaluation of safety and efficacy was based on key parameters, including drug bioavailability, the extent of BBB penetration, therapeutic outcomes, and adverse effects. Specific outcomes such as improved neuronal survival, behavioral enhancements in preclinical models, and patient-reported outcomes in clinical studies were highlighted to assess the translational potential of these technologies.

Results

Included studies

The initial search yielded 1,324 articles. After removing duplicates and unrelated studies, the remaining articles underwent full-text screening based on the pre-established inclusion and exclusion criteria. Ultimately, 9 studies met the

eligibility criteria and were included in the final review.

Key findings

The selected studies demonstrated promising advances in nanotechnology-based drug delivery systems for neurodegenerative diseases. Notably, RMT and exosome-based delivery emerged as the most effective mechanisms for crossing the BBB. Several studies highlighted that lipid-based nanoparticles improve drug bioavailability and target precision, leading to enhanced neuronal survival and reduced neuroinflammation. Additionally, AuNPs were shown to offer potential neuroprotective benefits due to their tunable properties. Ultrasound-mediated BBB opening was found to enhance drug delivery efficiency, while magnetic nanoparticles (MNPs) provided a controllable and targeted approach for delivering therapeutic agents to specific brain regions. Preclinical models consistently indicated improved cognitive and motor function with nanotechnology-based interventions, while early clinical trials reported increased patient tolerance and minimal adverse effects. These findings underscore the potential of nanotechnology to overcome BBB challenges and advance therapeutic options for neurodegenerative diseases.

Discussion

The development of nanotechnology for targeted drug delivery in neurodegenerative diseases is progressing rapidly, with several approaches advancing from preclinical models to early-phase clinical trials. Lipid-based nanoparticles and exosomes have demonstrated promising efficacy in delivering therapeutic agents across the BBB, improving neuronal survival and reducing disease progression in Alzheimer's and Parkinson's models [7]. Magnetic nanoparticles and ultrasound-mediated delivery are emerging as innovative techniques to enhance targeting precision and BBB permeability. While many strategies show potential in controlled environments, further clinical validation is required to establish long-term safety, efficacy, and scalability for widespread clinical use [8].

Lipid-based and nanoscale drug delivery systems, such as lipid nanoparticles (LNPs), nanoemulsions, polymeric micelles, and dendrimers, offer several advantages in overcoming the difficulties associated with treating neurodegenerative diseases. These systems focus on improving the stability, solubility, release profile, and overall effectiveness of the drugs they carry. In this context, functionalized nanoparticles and plant-derived extracellular vesicles (PEVs) are becoming increasingly important due to their ability to cross the blood-brain barrier and deliver their payloads precisely to the target areas in the brain [9]. Recent studies have shown that these advanced delivery systems can significantly enhance drug bioavailability and therapeutic outcomes, aligning with findings from other reports on brain-targeted therapies.

Lipid-Based Nanoparticles (LNPs) and nanoemulsions

LNPs have gained significant attention as a promising drug delivery system due to their ability to encapsulate both hydrophilic and lipophilic compounds, protecting them from degradation. These nanoparticles are often modified with surface coatings that improve their targeting capability and BBB penetration. For example, LNPs can be functionalized with ligands such as transferrin (Tf) or Angiopep-2, both of which are known to bind to receptors on endothelial cells and facilitate the crossing of the BBB [10]. LNPs have shown great promise in the delivery of mRNA vaccines and gene therapies, but their potential for delivering small molecules and biologics for neurodegenerative diseases is also being extensively explored.

In addition to LNPs, nanoemulsions are another lipid-based carrier system that has gained popularity for brain-targeted drug delivery. Nanoemulsions are composed of oil and water phases stabilized by surfactants that form nanometer-sized droplets. These droplets can significantly improve the solubility and bioavailability of poorly water-soluble drugs while also reducing toxicity. The size of the droplets allows them to penetrate biological barriers like the BBB, enhancing the delivery of both lipophilic and hydrophilic compounds to the brain. Nanoemulsions loaded with drugs such as empagliflozin have demonstrated anti-inflammatory and neuroprotective effects, showing promise for treating neurodegenerative diseases like Alzheimer's and Parkinson's. In comparison to traditional delivery systems, nanoemulsions have demonstrated superior drug bioavailabili-

ty and a reduced risk of systemic toxicity in several recent clinical investigations [11].

Polymeric micelles and nanogels

Polymeric micelles are self-assembled structures made from amphiphilic block copolymers, forming nanoscale assemblies with hydrophobic cores that encapsulate drugs and hydrophilic coronas that control pharmacokinetics. These micelles provide significant advantages in terms of solubilizing poorly water-soluble drugs and improving their bioavailability. They also have excellent drug release control, which is especially beneficial for maintaining therapeutic levels over extended periods. Furthermore, the surface of these micelles can be functionalized with cell-penetrating peptides (CPPs) or specific ligands that target the brain, improving their ability to cross the blood-brain barrier (BBB) and reach brain tissues [12].

In the context of neurodegenerative diseases, such as Alzheimer's and Parkinson's, polymeric micelles have been shown to enhance the delivery of drugs that can target disease-modifying pathways, such as those involved in amyloid-beta (Aβ) accumulation, tau phosphorylation, and neuroinflammation [13]. Studies have demonstrated that polymeric micelles loaded with siRNA targeting beta-secretase (BACE1) or tau proteins can reduce the accumulation of amyloid plaques or tau tangles in animal models of AD, thereby improving cognitive function [14]. However, these findings are yet to be validated in large-scale human trials, emphasizing the need for further clinical research to confirm their efficacy and safety.

Additionally, nanogels-nanoscale polymeric networks that can encapsulate and release bioactive compounds-offer significant advantages in terms of encapsulation efficiency, surface modification, and controlled drug release. Nanogels have been extensively researched for their ability to deliver both hydrophilic and hydrophobic drugs and biologics, including proteins, nucleic acids, and peptides. Their structure allows for high drug loading, and they can be easily modified with targeting moieties to enhance specificity for brain tissues. Nanogels have shown great potential in treating neurological diseases by enhancing drug stability and ensuring sustained release, which is critical for treating chronic conditions like AD and PD. Compared to polymeric micelles, nanogels offer better encapsulation efficiency and can deliver a broader range of therapeutic agents, as highlighted by recent comparative studies [13].

Extracellular Vesicles (EVs) and Plant-Derived Vesicles (PEVs)

Plant-derived extracellular vesicles (PEVs) have also emerged as a promising class of drug delivery systems. PEVs, which can be derived from sources like grapefruit, lemon, and carrot, are naturally equipped with membrane proteins that facilitate the crossing of the blood-brain barrier. These vesicles can encapsulate bioactive molecules, including small RNAs and proteins, and have demonstrated potential in reducing neuroinflammation, a hallmark of neurodegenerative diseases like AD and PD. PEVs have shown efficacy in delivering therapeutic agents across the blood-brain barrier, providing an exciting avenue for treating neurodegenerative diseases [15].

In particular, PEVs are believed to hold promise for delivering microRNAs (miRNAs), which can regulate gene expression in the brain. MiRNAs, such as those involved in amyloid precursor protein (APP) processing, tau phosphorylation, and neuroinflammation, play critical roles in the pathogenesis of AD. By utilizing PEVs to deliver therapeutic miRNAs, researchers are exploring novel ways to modulate gene expression and alter disease progression. Studies have shown that miRNAs carried by PEVs can influence the expression of genes that regulate inflammation, neuronal apoptosis, and synaptic dysfunction [16]. Future studies should investigate the long-term safety and stability of PEVs, particularly in chronic administration scenarios, as current evidence is limited.

Exosomes, a specific type of extracellular vesicle naturally secreted by cells, have also become a focus of research for drug and gene delivery. Exosomes possess unique properties, such as the ability to cross the blood-brain barrier, biocompatibility, and low immunogenicity. By loading exosomes with therapeutic nucleic acids, such as siRNA or miRNA, researchers can target key proteins involved in AD and other neurodegenerative diseases. Exosomes derived from specific cell types, such as dendritic cells or mesenchymal stem cells, can be genetically engineered to deliver specific thera-

peutic agents to the brain, enabling a highly targeted and efficient approach to therapy [17].

Functionalized nanoparticles for brain targeting

The development of functionalized nanoparticles has been a significant area of research aimed at improving the delivery of drugs to the brain. Functionalization refers to the modification of the surface properties of nanoparticles to enhance their ability to cross the blood-brain barrier and target specific cells or tissues. This can be achieved through the attachment of targeting ligands, such as antibodies, peptides, or cell-penetrating peptides (CPPs), to the surface of nanoparticles. By using these ligands, researchers can direct the nanoparticles to specific receptors on neuronal cells, improving the targeting of drugs to the brain and increasing therapeutic efficacy [18].

For example, RVG peptide, derived from the rabies virus, has been widely used to enhance the ability of nanoparticles to cross the blood-brain barrier via receptor-mediated endocytosis. By functionalizing nanoparticles with RVG peptide, researchers can achieve enhanced brain penetration and targeted delivery of therapeutic agents to neurons. Similarly, functionalizing nanoparticles with transferrin or other receptor-binding ligands has been shown to improve the targeted delivery of drugs to brain tumors, such as gliomas, by targeting transferrin receptors on endothelial cells of the BBB [19].

Another promising strategy involves the use of dendrimers, which are highly branched, nanosized particles that offer precise control over size, surface charge, and drug loading. Dendrimers are often functionalized with specific ligands to target the brain, and they offer enhanced drug release rates compared to other nanoparticles due to their unique architecture. Studies have shown that dendrimers can successfully deliver both small molecules and nucleic acids to the brain, opening new possibilities for gene therapy and targeted drug delivery in neurodegenerative diseases.

Gene delivery and nucleic acid-based therapies for neurodegenerative diseases

Gene therapy and nucleic acid-based therapies are emerging as promising strategies for treating neurodegenerative diseases like Alzheimer's and Parkinson's. These therapies aim to target specific genes or proteins that are implicated in disease progression. However, delivering nucleic acids, such as siRNA, microRNA (miRNA), antisense oligonucleotides (ASOs), and plasmid DNA (pDNA), to the brain remains a significant challenge due to the difficulty in crossing the blood-brain barrier [20].

Functionalized nanoparticles, including liposomes, dendrimers, and polymeric micelles, offer a potential solution to this challenge. By encapsulating nucleic acids in nanoparticles and modifying their surface with specific targeting ligands, researchers can increase the specificity and efficiency of nucleic acid delivery to the brain. For example, polymeric micelles functionalized with cell-penetrating peptides (CPPs) or targeting ligands such as lactoferrin have been shown to enhance the delivery of siRNA and other therapeutic genes to the brain [20].

One of the most promising applications of gene therapy for neurodegenerative diseases is the use of small interfering RNA (siRNA) and microRNA (miRNA) to silence genes involved in the pathogenesis of diseases like Alzheimer's. For instance, miRNA-loaded nanoparticles have been used to target beta-secretase (BACE1), a key enzyme involved in the production of amyloid-beta plaques, a hallmark of Alzheimer's disease. Delivery of siRNA targeting BACE1 has been shown to reduce amyloid-beta levels and improve cognitive function in animal models of Alzheimer's disease [19].

Additionally, antisense oligonucleotides (ASOs) have shown promise in targeting tau protein, which accumulates in tauopathies like Alzheimer's disease and frontotemporal dementia. Clinical trials are currently underway to evaluate the efficacy of ASOs, such as the drug MAPT Rx, in reducing tau levels and improving cognitive function in patients with Alzheimer's. The ability to deliver these therapeutic nucleic acids to the brain is critical for the success of gene therapies in neurodegenerative diseases.

Exosomes and Artificial Vesicles (AVs) in drug delivery

Exosomes, small vesicles secreted by cells, have become a focal point for drug and gene delivery due to their ability to naturally cross

the blood-brain barrier and their biocompatibility. Exosomes can encapsulate various therapeutic agents, including proteins, small molecules, and nucleic acids. While exosomes hold great promise, their production and isolation methods are still under development, and there is a need for improved understanding of their safety and long-term effects [19].

Artificial vesicles (AVs), including liposomes and synthetic vesicles, represent an engineered alternative to natural exosomes. These vesicles can be precisely designed to encapsulate therapeutic agents and can be modified with specific targeting ligands to enhance their brain targeting capabilities. Liposomes, for example, have been used as delivery vehicles for a wide range of drugs and have been approved by regulatory agencies for use in clinical settings. Advances in the functionalization of AVs with cell-penetrating peptides (CPPs) and targeting ligands have significantly improved their ability to deliver drugs to the brain [21].

While nanotechnology-based drug delivery systems present a promising frontier for treating neurodegenerative diseases, several limitations persist. One primary concern is the potential for immunogenicity and off-target effects, which could lead to adverse outcomes. Moreover, the scalability of manufacturing and ensuring batch-to-batch consistency remain substantial challenges. The long-term impact of these nanoparticles on brain tissue and overall neurophysiology is not yet fully understood, warranting comprehensive longitudinal studies.

Conclusion

The development of advanced drug delivery systems, including lipid-based nanoparticles, extracellular vesicles, and functionalized nanoparticles, represents a major step forward in the treatment of neurodegenerative diseases. These systems provide the ability to deliver therapeutic agents across the blood-brain barrier, a key challenge in treating diseases like Alzheimer's and Parkinson's. By incorporating targeted functionalization strategies, such as the use of cell-penetrating peptides and receptor-binding ligands, researchers are improving the precision and efficacy of brain-targeted therapies.

Disclosure of conflict of interest

None.

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