RESEARCH PAPER

Nanocarrier-Mediated Targeted Drug Delivery Across the Blood–Brain Barrier for Neurodegenerative Disorders

Yogesh Kumar[1*], Dr Priti Patel[2], Suryanarayana Reddy Kovvuri[3], Shruti Tyagi[4], Dr. Hemang Shah[5], Pranit Saraswat[6], Bikram Sarkar[7]

[1*]Professor, Physiology, AIIMS PATNA, PATNA, BIHAR Email id: dryogeshk@aiimspatna.org, Orcid Id: 0000-0002-9712-4290

[2]Associate Professor, Department of Pharmacology, University of Mumbai, Thane, Mumbai- 421003, India, Email Id: patel.priti.28@gmail.com, Orcid Id: https://orcid.org/0000-0002-0073-2637

[3]Postgraduate, General Medicine, Saveetha Medical College, Chennai, Tamil Nadu Email id: drsurya9999@gmail.com, Orcid Id: 0009-0001-7636-7138

[4]Associate Professor, Department of Zoology, Indira Gandhi University, Meerpur, Rewari, Haryana ORCID ID : 0000-0003-4473-106X, Mail ID - shruti.zoology@igu.ac.in

[5]Professor and Head Department of Psychiatry Specialization : Psychiatry Dr N D Desai Faculty of Medical Science and Research, Dharmsinh Desai University (DDU), Gujarat City Nadiad, Pin-387001, Orcid ID: 0009-0009-1727-6357, Email id : drhemangshah@yahoo.co.in

[6]Associate Professor Pharmaceutical Chemistry Saraswati College of Pharmacy, Gharaun, Mohali pranitsaraswat41@gmail.com

[7]Student M.Pharm(Pharmacology) Specialization: Pharmacology Global College Of Pharmaceutical Technology, Palpara, Krishnanagar, Nadia, West Bengal, India, Krishnanagar, 741102 Email ID: bikramsarkar629794@gmail.com

Abstract

Neurodegenerative disorders (NDs), including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS), represent a major global healthcare burden due to their progressive nature and limited therapeutic options. One of the primary challenges in treating these disorders is the presence of the blood–brain barrier (BBB), which restricts the entry of most therapeutic agents into the central nervous system (CNS). Nanocarrier-mediated drug delivery systems have emerged as promising approaches for overcoming BBB-associated limitations and improving targeted CNS therapeutics. This review comprehensively discusses the structure and transport mechanisms of the BBB, pathophysiological features of major neurodegenerative diseases, and recent advancements in nanocarrier-based delivery systems. Various nanoplatforms, including lipid-based, polymeric, inorganic, biomimetic, and hybrid nanocarriers, are highlighted for their ability to enhance BBB penetration, improve drug bioavailability, and achieve controlled and site-specific delivery. Additionally, targeted delivery strategies such as ligand-mediated transport, surface functionalization, stimuli-responsive systems, and intranasal delivery approaches are discussed. The review further examines therapeutic applications, preclinical evaluation methods, clinical translation challenges, regulatory perspectives, and future directions involving personalized nanomedicine, artificial intelligence-assisted design, and multifunctional smart nanoplatforms. Overall, nanotechnology-based CNS drug delivery offers substantial potential for improving therapeutic outcomes and advancing precision treatment strategies for ND.

Keywords: Blood–brain barrier; Nanocarriers; Neurodegenerative disorders; Targeted drug delivery; Nanomedicine

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1. Introduction

Neurodegenerative disorders (NDs) are a class of disorders that are progressive, debilitating, and involve a gradual loss of structure or function of neurons in the central nervous system (CNS). The most common NDs are Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). Recognized as significant public health issues worldwide, these disorders are growing in prevalence, are progressive and lack effective curative therapies. Strikingly, neurodegenerative diseases are increasingly prevalent in the world due to aging populations, environmental factors, genetic susceptibility, and lifestyle risks [1]. This gradual decline is a major limitation in cognitive, motor and behavioral functions leading to a decrease in patient's life quality and dependency on long term medical and social care.

The socioeconomic impact of neurodegenerative diseases is significant and is increasing at an ever-increasing rate. Apart from the direct healthcare costs associated with diagnosis, hospitalization, treatment, rehabilitation and co-ordinating patient care, these diseases incur a huge amount of indirect costs through loss of productivity, disability, stress on caregivers and premature mortality [2]. In addition, social and economic inequalities may affect access to care, medication adherence, and health outcomes, further increasing the social and economic burden for the individual and their caregivers with the disease [3].

*Author for Correspondence dryogeshk@aiimspatna.org

Although there has been significant progress in neuroscience and pharmacological research, most of the therapeutic interventions available nowadays are still symptomatic, and do not stop or reverse the progression of the disease. Conventional drugs are typically poorly bioavailable, poorly permeable to the brain, quickly cleared from systemic circulation and have undesirable side effects – all of which limit the therapeutic value of conventional drugs in CNS disorders.

The Blood-Brain Barrier (BBB) is one of the most difficult barriers in the effective treatment of neurodegenerative disorders, which is an extremely selective physiological barrier that regulates molecular trafficking between the circulation and the brain. The BBB consists mainly of closely apposed endothelial cells, astrocytes, pericytes, and basement membrane components, which together preserve the cerebral homeostasis [4]. The active transport proteins, including P-glycoprotein, in endothelial cells block many drugs from entering and remaining in brain tissue and tight junction proteins block paracellular movement within endothelial cells. While the BBB is important to protect neural tissues from toxins and pathogens, it is also a formidable barrier to CNS drug delivery, as the vast majority of all large biomolecules and most small-molecule drugs cannot efficiently cross the barrier [4]. As a result, many potentially effective neurotherapeutics are not able to reach therapeutic levels in the brain.

The development of nanocarriers has been considered as a novel approach to tackle the limitations associated with the BBB and enhance the targeted delivery of therapeutic agents to the CNS in recent years. Nanocarriers such as liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles and inorganic nanoparticles have distinctive physicochemical properties that improve the solubility, stability, bioavailability, and BBB permeation of the drug [5]. They can be modified at the surface to enhance receptor-mediated uptake, and specific targeting ligands can be attached for site-specific targeting in diseased brain tissue, in order to achieve desired results. Nanocarrier-mediated systems have superior pharmacokinetic properties, controlled drug release, less systemic toxicities, and increased therapeutic efficacy than other conventional methods of drug delivery. Hence, nanotechnology has become an area of great interest in CNS drug delivery for the treatment of neurodegenerative diseases.

Research Objectives

1. To evaluate the role of the blood–brain barrier in limiting CNS drug delivery for neurodegenerative disorders
2. To analyze nanocarrier-based strategies for targeted drug delivery across the blood–brain barrier
3. To examine the therapeutic potential and translational challenges of nanocarrier-mediated neurotherapeutics

2. Pathophysiology of NDs and Therapeutic Targets

NDs involve a gradual impairment of the function of neurons and a permanent destruction of neurons in the CNS that leads to cognitive, behavioural and motor impairments. Among the most common neurodegenerative diseases, AD, PD, HD, ALS and MS share some common pathological mechanisms including protein aggregation, oxidative stress, mitochondrial dysfunction, neuroinflammation, and disruption of the BBB [6]. Such multifactorial pathological events help the progression of the disease and are great challenge for therapy.

The major pathological features of AD are extracellular deposits of 'amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles' consisting of hyperphosphorylated tau proteins. These abnormalities interfere with the normal function of the neurons, cause oxidative stress and activate inflammatory processes leading to speeded up neuronal degeneration. Furthermore, PD is primarily linked to substantia nigra dopaminergic neuron degeneration and to the accumulation of α-synuclein protein in Lewy bodies, causing problems with motor coordination and mitochondrial dysfunction. The injury of neurons in PD is further exacerbated by oxidative stress and neuroinflammation [6].

The mutation of the huntingtin gene in HD leads to the production of mutant huntingtin protein which accumulates within the neurons, and which interferes with the regulation of transcription, synaptic signaling, and mitochondrial activity. This ultimately gives rise to neuronal toxicity and to the gradual motor and cognitive deterioration. ALS is characterized by the degeneration of upper and lower motor neurons, with excitotoxicity, excessive glutamate signaling, mitochondrial dysfunction and oxidative stress all playing a role in the progressive muscle weakness and paralysis seen in ALS. In addition, abnormal accumulation of proteins such as 'SOD1 and TDP-43' are suspected to play a role in ALS pathogenesis.

MS is unique among other NDs in that it is an autoimmune disease in which autoreactive immune cells cross the BBB and attack the myelin sheath which surrounds the neuronal axons and causes demyelination and impaired neuronal conduction [7] Chronic neuroinflammation and BBB dysfunction are key to disease pathogenesis. There is also growing evidence that BBB impairment plays a key role in the pathogenesis of various NDs, through the mechanisms of increased neuroinflammation and impaired clearance of toxic proteins [8]. As a result, therapeutic targets like protein aggregation, oxidative stress pathways, inflammatory mediators, mitochondrial dysfunction and BBB restoration have become of great interest for the development of advanced neurotherapeutic strategies (Figure 1).

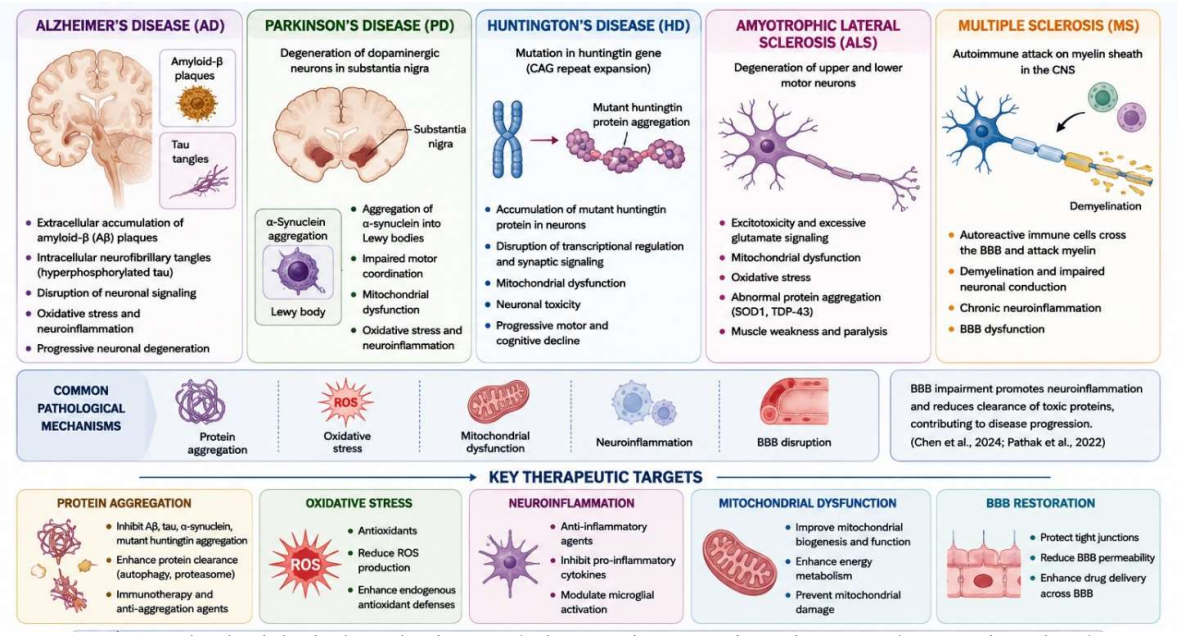

Figure 1. Pathophysiological Mechanisms and Therapeutic Targets in Major Neurodegenerative Disorders

3. Structure, Function, and Transport Mechanisms of blood–brain barrier

The BBB is a highly specialized and selectively permeable physiological barrier between CNS and systemic circulation. It is essential to preserve neuronal tissue from harmful substances in the blood, from dangerous pathogens and toxins and from the disruption of the cerebral homeostasis [9]. The BBB is crucial to maintain neuronal stability and normal brain function, but also poses a significant challenge in delivering therapeutic agents to the CNS, owing to its restricted permeability. Hence, knowledge of BBB structure, functions and transport mechanisms is crucial for the design of efficient nanocarrier-based drug delivery systems for neurodegenerative diseases.

3.1 Cellular Architecture of the BBB

The BBB is a highly organized neurovascular unit composed of endothelial cells, astrocytes, pericytes and the basement membrane [10]. It is composed structurally of brain microvascular endothelial cells and is tightly juxtaposed with each other by junctional proteins including 'claudins, occludins, and junctional adhesion molecules'. These tight junctions play a very significant role in limiting the paracellular transport and, as such, the selective permeability of the BBB. BBB endothelial cells have very few fenestrations and have little pinocytic activity compared to peripheral endothelial cells, which results in restricted transport of molecules by nonselective passage [9].

The role of astrocytes in BBB maintenance is essential and their special end-feet processes around the cerebral capillaries have essential roles. These cells maintain ion balance, exchange nutrients and influence neuronal metabolism, and a role in maintaining endothelial tight junction integrity. The pericytes that are located within the vascular basement membrane regulate vascular stability, angiogenesis, cerebral blood flow and immune signaling. They also play a role in regulating BBB permeability and maintaining neurovascular homeostasis [11]. The basement membrane supports the structure and enables communication between the endothelial cells, the astrocytes and the pericytes, thus helping to stabilize the neurovascular unit.

3.2 Physiological Functions of the BBB

It is one of the most important functions to maintain the homeostasis of the brain by controlling the movement of nutrients, ions, neurotransmitters and metabolic waste products between the systemic circulation and brain tissues. This is important for maintaining the excitability of neurons, the signaling between synapses, and normal brain function [12]. Moreover, the BBB prevents changes in the composition of blood in affecting the neuronal microenvironment.

The other crucial role of the BBB is immune regulation. The BBB serves as an immunological barrier to prevent peripheral immune cells, pathogens and inflammatory mediators from entering into the CNS. The BBB regulates immune surveillance and inflammatory responses and shields neural tissues from overactive neuroinflammation and immune mediated damage. This protective mechanism is essential for the stability of neurons and to avoid pathological CNS inflammation.

3.3 Mechanisms of Transport Across the BBB

There are multiple ways to transport molecules across the BBB that are highly regulated and serve to selectively transport molecules across the BBB. Passive diffusion is one of the simplest pathways for transport and is the route used by small (lipophilic) molecules, such as oxygen and carbon dioxide, to move across endothelial membranes from a region of high concentration to one of low concentration. Most

*Author for Correspondence dryogeshk@aiimspatna.org

molecules and macromolecules, however, are unable to passively cross the BBB. Essential nutrients, like glucose, amino acids and vitamins are transported by carrier-mediated transport, involving special transporter proteins on the membranes of endothelial cells. Receptor-mediated transcytosis, on the other hand, allows larger biomolecules such as insulin, transferrin and peptides to be transported by binding to a receptor, internalization of the receptor-ligand complex and the subsequent transport via the vesicles across endothelial cells [13]. The electrostatic forces between the positively charged molecules and negatively charged endothelial membranes have been found to facilitate uptake and translocation of the molecules within the cells, a process called adsorptive-mediated transcytosis. Moreover, the cell mediated transport of therapeutic agents across the BBB to CNS is also performed by cells of the immune system, including macrophages and monocytes.

3.4 BBB Dysfunction in Neurodegenerative Diseases

The dysfunction of the BBB is emerging as an important player in the pathogenesis and progression of NDs. The BBB leakage and barrier disruption, due to endothelial damage, impairment of transporter activity, and elevated BBB permeability, may result in neuroinflammation, oxidative stress, and the accumulation of toxic proteins inside the brain [8]. The dysfunction of the BBB results in decreased clearance of Amyloid-β, which in AD results in the accumulation of Aβ in the neural tissue. In the same way, BBB disruption allows infiltration of inflammatory mediators and immune cells into the brain in PD and MS, leading to neuronal injury and/or demyelination. Hence, the investigation of BBB dysfunction has become an attractive therapeutic approach to enhance the delivery of drugs to the CNS and delay in progression of neurodegenerative diseases.

Table 1. Structural, Functional, and Transport Characteristics of the BBB in CNS Drug Delivery

BBB Aspect	Key Components	Role in CNS Drug Delivery	References
Cellular architecture	Endothelial cells, astrocytes, pericytes, basement membrane	Maintains BBB integrity and selective permeability	Benz & Liebner, [9]
Physiological functions	CNS homeostasis and immune regulation	Protects neural tissues but limits therapeutic entry	Wu et al [12]
Transport mechanisms	Passive diffusion, carrier-mediated transport, receptor-mediated transcytosis, adsorptive-mediated transcytosis, cell-mediated delivery	Enables selective molecular transport across the BBB	Lalatsa & Butt, [13]
BBB dysfunction	Tight junction disruption, endothelial injury, impaired transporters, increased permeability	Promotes neuroinflammation, oxidative stress, and toxic protein accumulation	Chen et al., [8]
Therapeutic relevance	BBB-targeted nanocarrier delivery	Enhances CNS drug delivery for neurodegenerative disorders	Benz & Liebner, [9]

4. Nanocarriers for BBB Penetration

Nanocarriers have become one of the most promising strategies to overcome the barrier properties of BBB and deliver drugs to the CNS. These effects restrict the effectiveness of traditional therapies for treating NDs because the BBB is extremely impervious to their penetration. Nanocarriers have distinctive physicochemical properties that can lead to improved drug stability, controlled release, prolonged circulation time, targeted delivery, and increased BBB permeability [14]. The nanocarrier system shows great promise to achieve efficient CNS drug delivery, such as lipid-based, polymeric, inorganic, biomimetic, and hybrid nanoplatforms.

4.1 Design Principles of Nanocarriers

Nanoparticles of sizes smaller than 200 nm show better BBB penetration properties and less reticuloendothelial system clearance [12]. Particles' shape also has an effect on the behaviour of uptake and circulation in the cells, and the surface charge influences on interaction with the endothelial membranes. Often, positively charged nanocarriers exhibit better cell internalization and adsorption because they have electrostatic interactions with negatively charged surfaces of the BBB.

In addition, biocompatibility and biodegradability are important factors to consider in the design of nanocarriers. Biodegradable nanomaterials lower the toxicity and ensure metabolic clearance after the drug delivery, which is safe for long term use. The use of biosafeby materials like lipids, biodegradable polymers, and naturally derived biomaterials is popular for enhancing biosafety and retaining therapeutic efficacy [15]. So, making nanocarriers effective to penetrate the BBB and deliver therapeutic agents to the brain in a targeted way demands optimisation of their design.

4.2 Lipid-Based Nanocarriers

The enhanced BBB penetration and cellular uptake [16] of lipid-based nanocarriers, thanks to their low toxicity, high biocompatibility, and structural resemblance with the biological membranes, makes them a promising approach for CNS drug delivery. Liposomes, which are vesicles made from phospholipids, have the ability to carry both hydrophilic and lipophilic drugs and can be targeted and delivered for a longer period of time by surface modifications like PEGylation [17], are among

these systems. The controlled release property, increased stability and decreased systemic toxicity are just some of the advantages of SLN, while the flexible lipid matrix makes them superior in drug loading capacity and their sustained release properties make them superior to SLNs [18,19].

4.3 Polymeric Nanocarriers

The high stability, biodegradability, and controlled drug release capabilities of polymeric nanocarriers have made them an attractive choice for blood–brain barrier (BBB) targeting [15]. Polymeric nanoparticles enable to deliver the drug for an extended period of time and target it specifically, and polymeric micelles enhance the penetration of the BBB and solubility of hydrophobic drugs due to their amphiphilic core–shell structure. Furthermore, dendrimers have highly branched structures with multiple functional groups which allows the efficient loading of drug molecules, their surface modification, controlled release and enhanced cellular uptake in the neural tissues.

4.4 Inorganic Nanocarriers

The optical, electronic and magnetic properties of inorganic nanocarriers are distinct and can be used for therapeutic and diagnostic purposes. Gold nanoparticles are highly biocompatible, have a tunable surface chemistry, and have imaging properties, all of which make them ideal for targeted CNS delivery. The silica nanoparticles have high surface area, structural stability and controlled drug release properties. External magnetic fields can be used to steer magnetic nanparticles towards specific brain regions for targeted delivery, while quantum dots have unique fluorescent properties, allowing for imaging and therapeutic monitoring within the CNS.

4.5 Biomimetic and Biological Nanocarriers

Biomimetic and biological nanocarriers aim to simulate the natural biological systems, which further improves its biocompatibility, immune evasion and penetration to the CNS for targeted delivery of drugs to CNS [20]. Exosomes and EVs are naturally occurring nanoscale vesicles that have the ability to carry proteins, lipids, and nucleic acids across the BBB with low immunogenicity and therefore are highly attractive to use in neurotherapeutics. Likewise, cell membrane coated nanoparticles employ cell membranes from erythrocytes, leukocytes, or cancer cells to prevent clearance by the immune system, extend systemic circulation and enhance targeting potential [21]. Virus-like nanoparticles with the virus-mimicking structure but without its genetic material further improve the intracellular delivery thanks to their characteristics.

4.6 Hybrid Nanocarrier Systems

Hybrid nanocarrier systems are a combination of several material components of nanotechnology that combine the best aspects of multiple delivery systems into a single system. The multifunctional nanocarriers can be made from various materials to achieve better targeting efficiency, drug-loading capacity and controlled release properties, as well as stability. Further, stimuli-responsive hybrid systems can be designed to respond to an environmental stimulus (pH, temperature, enzymes, magnetic field) to induce site specific therapeutic release within diseased neural tissues [14]. The multifunctional nanoplatforms have great potential in precision medicine and targeted treatment of neurodegenerative diseases.

5. Strategies for Targeted Drug Delivery Across the BBB

The delivery of drugs to the CNS via targeted delivery across the BBB has become an important approach to enhance the therapeutic potential of the treatment of NDs. The BBB is very permeable to some drugs and very impermeable to others; this makes it difficult to get sufficient levels of conventional therapeutics into the CNS. Thus, advanced nanocarriers targeted approaches have been developed to enable efficient BBB crossing, increase the site-specific accumulation of drugs, and reduce the side effects of the system [22]. Of these strategies, ligand-mediated targeting is one of the most widely explored strategies. The strategy involves the use of compounds that are ligands for receptors that are highly expressed on endothelial cells of the BBB that can stimulate receptor-mediated transcytosis. Usually used ligands are transferrin, lactoferrin and apolipoprotein E (ApoE) which are much available on the receptors of brain capillaries and help the nanocarriers to be transported into the brain tissues effectively [23]. Peptides and monoclonal antibodies, moreover, have been noted for their high specificity and receptor-binding affinity and, for this reason, have been found to be promising as target specific [24].

An additional improvement of the BBB penetration and systemic stability is achieved by surface functionalization of nanocarriers. PEG coating (PEGylation) is a process that increases circulation time by minimizing immune recognition and fast clearance by the reticuloendothelial system. PEGylated nanocarriers have been shown to have superior stealth features, stability and localization in the brain [25]. In addition, the modifications to the nanocarriers by conjugation with targeting ligands, surfactants, and cell penetrating molecules can significantly enhance receptor-mediated uptake and delivery into the interior of the cell.

In recent years, new developments have also resulted in the creation of stimuli-responsive nanocarriers of drugs that release their contents either internally or externally when stimulated. pH-sensitive systems deliver therapeutic agents during acidic pathological conditions; while redox-sensitive nanocarriers take advantage of the high amount of intracellular glutathione. Enzyme-responsive systems are triggered by the enzymes that are found in neurodegenerative tissues, which increases the specificity of delivery. Further, magnetic and ultrasound-activated systems allow for targeted drug delivery from the outside and

transient increase in BBB permeability to allow efficient delivery of therapeutics into the CNS [26].

The delivery through the nose or "intranasal" or nose-to-brain has been receiving much attention as a non-invasive way of circumventing the BBB. Intranasal delivery of therapeutics using nanocarriers directly to the brain via the olfactory and trigeminal pathways offers bioavailability advantages and decreases systemic exposure [27]. Natural toxins and animal venoms are the source of CPPs that show high translocation efficiency and are able to translocate therapeutics into cells across biological membranes [28]. Together, these sophisticated targeting strategies hold great promise for improving CNS drug delivery and developing new nanomedicine therapy strategies for neurodegenerative diseases (Figure 2).

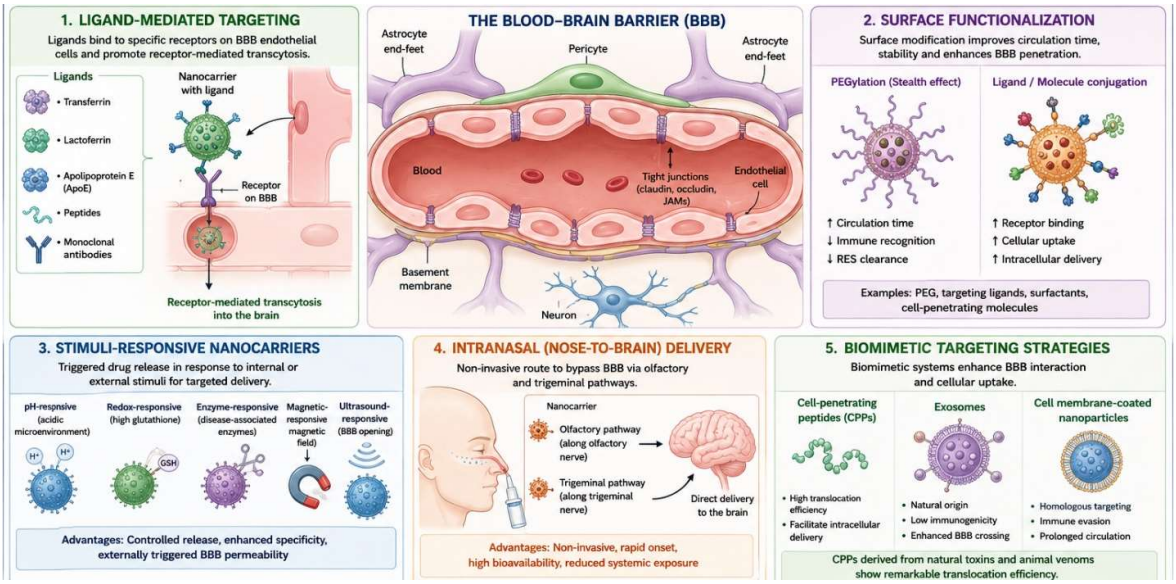

Figure 2. Advanced strategies for Targeted Drug Delivery Across the BBB

6. Therapeutic Applications in Neurodegenerative Disorders

The use of nanocarrier-based drug delivery system has been shown to have a significant therapeutic application in the treatment of NDs because of its ability to enhance the penetration of BBB, increase drug bioavailability and targeted delivery to diseased neural tissues. These innovative nanomedicine platforms enable the identification of novel therapeutic strategies that overcome challenges of traditional therapies such as low penetration into the CNS, systemic toxicity, and rapid degradation of drugs [29]. As a result, nanocarrier therapies are actively being investigated for the treatment of 'AD, PD, HD, ALS and neuroinflammation-related neurodegeneration'.

In AD, nanocarrier-based therapeutics are mainly targeted at the reduction of aggregation of amyloid-β, suppression of neuroinflammation, and neuronal survival. Medications that target amyloid targets can be delivered via nanoparticles to increase concentration in the brain and decrease peripheral toxicity. Recent research has also shown that BBB-permeable nanomedicines are also effective in inhibiting neuroapoptosis and inflammatory responses, improving cognitive function and slowing the progression of the disease [30]. Nanocarriers to deliver anti-inflammatory therapeutic agents that can modulate microglial activation and oxidative stress have demonstrated promising neuroprotective effects in models of AD [31].

The primary targets of nanotherapeutic strategies against PD are restoration of dopaminergic signaling, reduction of oxidative stress and inhibition of α-synuclein aggregation. Nanocarriers containing dopamine or dopamine agonists are more stable and can deliver more efficient targeted delivery to the substantia nigra, resulting in fewer side effects on the rest of the body and better motor function. In addition, use of neuroprotective nanomedicines, including antioxidants, growth factors, or anti-inflammatory agents, helps to decrease neuronal degeneration caused by oxidative stress and mitochondrial dysfunction. Other nanoscale delivery systems, such as extracellular vesicles, have also been shown to have the potential to deliver therapeutic molecules that inhibit the aggregation of α-synuclein and reduce neuroinflammation in PD [32].

However, nanocarriers have received considerable attention as nanocarriers for nucleic acid-based therapeutics like siRNA, antisense oligonucleotides, and CRISPR-associated gene editing systems in the field of HD and ALS. These therapies focus on diseased and harmful mutations in genes. The therapeutic stability, cellular uptake and BBB penetration are enhanced, and off-target effects are decreased with nanocarrier-mediated gene delivery [33]. Additionally, antioxidant, anti-apoptotic, and mitochondrial stabilizers have shown promise in slowing the degeneration of neurons and improving the survival of cells in HD and ALS.

There are also therapeutics under development for neuroinflammation and oxidative stress that have demonstrated therapeutic effects in several neurodegenerative diseases that are being investigated by nanomedicine. The production of reactive oxygen species, the release of inflammatory cytokines and the viability of the neurons can be decreased by the use of antioxidant loaded nanocarriers. These strategies are especially relevant, as chronic neuroinflammation and oxidative stress are hallmark physiological pathways involved in neurodegenerative disease processes.

Multifunctional NANO Carriers are capable of monitoring the disease, delivering targeted drugs and evaluating the therapeutic response, all in one. It has been recently shown that theranostic nanomedicine has great potential to enhance precision diagnosis and therapy of neurodegenerative and neurological disorders [34]. In summary, Nanocarrier-based therapy offers a revolutionary strategy for improving the delivery of therapeutic agents to the CNS and represents a promising approach to the treatment of NDs.

7. Preclinical Models and Evaluation Methods

Preliminary models and test strategies are critical to evaluating the safety, efficacy, and BBB permeability of nanocarrier-based therapeutics prior to clinical use. In vitro BBB models are frequently adopted for the initial screening due to the ability to set up controlled and repeatable environment for investigating nanoparticle transport and drug permeability. Static BBB models are usually endothelial cell monolayers cultured in transwell systems, while for dynamic models' fluid shear stress and multicellular interactions are introduced to better mimic physiological BBB conditions [35]. Recently, organ-on-chip platforms have become an advanced microfluidic system that can mimic the structure and function of the neurovascular unit. Nanomedicines are widely used to study their biodistribution, pharmacokinetics, therapeutic efficacy, and neurotoxicity in vivo animal models, including rodents and non-human primates, in the context of neurodegenerative diseases [36]. In addition, imaging methods like fluorescence imaging, magnetic resonance imaging (MRI), and positron emission tomography (PET) are employed to track the localization of nanoparticles, accumulation in the brain, and efficacy of therapeutic intervention in real time, which aids in the optimization and translation of nanotherapeutics directed towards the CNS [34].

8. Clinical Translation and Regulatory Perspectives

In recent years, the clinical translation of nanocarrier therapeutics for CNS disease has received enormous momentum from the many advances in nanomedicine, targeted drug delivery and approaches for crossing the BBB. Liposomal systems, polymeric nanoparticles, and lipid based nanocarriers are some of the nanomedicine systems that are being evaluated for pre-clinical and clinical development in the treatment of neurodegenerative diseases including AD, PD, glioblastoma and MS. Only a few nanoformulations have been approved for neurological applications, and many others are in the clinical development stage. These systems are designed to increase the therapeutic efficacy, increase brain delivery, decrease systemic toxicity, and give sustained drug release. Although promising in pre-clinical settings, the translation to the clinical setting is complicated by the complexity of the CNS environment and the inter-individual variability in response to treatment.

The clinical use of CNS nanomedicines is facing several challenges, including toxicological and safety issues. Nanoparticles can cause neuronal damage by causing oxidative stress, mitochondrial dysfunction, inflammation and disruption of neuronal signaling pathways. Another important issue is immunogenicity, as the composition, surface characteristics and dosage of the nanocarriers could lead to immune responses and/or hypersensitivity reactions. Furthermore, chronic toxicity and/or undesirable biological effects may occur if the nanoparticles are not biodegradable and accumulate in neural tissues or peripheral organs over time. Thus, detailed toxicological testing and extended biosafety assessment is needed prior to clinical use.

Another obstacle in the way of developing nanomedicines is manufacturing and scalability. 'Good Manufacturing Practice (GMP)' standards must be followed to achieve product quality, sterility, stability and batch-to-batch reproducibility in large scale production of nanocarriers. The size, surface charge and encapsulation efficiency of nanoparticles can have a profound impact on therapeutic activity and the safety profiles. Hence, the ability to consistently manufacture and to characterize the products is essential for commercialization.

CNS nanomedicines must meet the regulation guidelines set by the agencies like the 'United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA)'. The special physicochemical characteristics and polyfunctional nature of nanotherapeutics, however, make the evaluation and classification for the purposes of regulations challenging. The lack of universal acceptance of standard protocols of characterization, toxicity testing, and clinical evaluation of nanoparticles is still a major regulatory hurdle. Thus, harmonised regulations and internationally standardised assessment criteria are required to speed up the clinical translation of nanocarrier mediated neurotherapeutics for safe and effective use.

9. Current Challenges and Future Perspectives

Although substantial advances have been made in the field of nanocarrier-mediated drug delivery systems in the neurodegenerative diseases, there are still some challenges that hinder the successful translation and therapeutic effects of nanocarriers in neurodegenerative diseases. The issue of efficient transport of nanoparticles to the brain region and the potential for off-target accumulation in peripheral organs is one of the major challenges faced. Complex biological barriers, such as BBB, are one of the most important

obstacles to the efficient transport of nanoparticles into the brain region, and may lead to peripheral organs accumulation. The unintended biodistribution, immune activation, and non-specific cellular uptake may decrease therapeutic precision, and enhance systemic toxicity. Additionally, different disease pathologies, genetic backgrounds and patient-specific physiological traits require the creation of personalised and precision nanomedicine solutions to be able to adapt the treatment for each patient profile.

At the same time, the development of gene-editing technologies and RNA-based therapeutics, such as CRISPR-Cas systems, siRNA, and antisense oligonucleotides, has opened the door to the potential for correction of disease-associated genetic abnormalities and modulation of pathological pathways in neurodegenerative diseases. To ensure the delivery of these delicate biomolecules to the BBB, it is crucial to develop efficient nanocarrier systems that will shield them from degradation and help them reach their target with ease. These sophisticated systems have a lot of promise for more precise therapeutic targeting, fewer side effects, and more individualized therapeutic strategies for complicated neurodegenerative diseases.

10. Conclusion

The use of nanocarriers for targeted drug delivery has proven to be a very promising approach for addressing the drawbacks of traditional drug treatments against neurodegenerative diseases. The BBB, crucial for the homeostasis of the CNS, is still an important barrier in the way of effective therapy delivery. Recent progress in nanotechnology has led to the development of various nanocarrier systems that show potential to increase the penetration of the BBB, improve the stability of the carrier, and deliver targeted drugs to diseased neural tissues. Nanoplatforms have shown great promise for therapeutic application in a variety of diseases including AD, PD, HD, ALS, and MS, with therapeutic mechanisms including anti-inflammatory activity, drug release, gene delivery, and neuroprotection. Additionally, new multifunctional, stimuli-responsive nanocarriers that, along with precision medicine and theranostic strategies, are anticipated to enhance the efficacy of therapy and monitoring of disease. Biological barriers, toxicity, scale up for clinical translation, reproducibility, and regulatory standardization remain challenges, though. The advancement of nanomedicine, the emergence of artificial intelligence in designing new nanocarriers and the development of improved gene editing delivery systems could propel safer, more efficient, and clinically viable neurotherapeutic interventions against NDs to the next stage in their development.

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