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Targeting the Blood–Brain Barrier: Pharmaceutical Nanotechnology Approaches in Neurotherapeutics

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Abstract:

Crossing the blood–brain barrier (BBB) remains one of the greatest challenges in treating central nervous system (CNS) disorders, including Alzheimer's disease, Parkinson's disease, glioblastoma, and stroke. The BBB's tightly regulated architecture—comprising endothelial cells, pericytes, astrocytes, and multifunctional transport systems—limits the penetration of most therapeutics, from small molecules to biologics. Nanotechnology has emerged as a transformative approach to overcome these delivery barriers by enabling precise engineering of size, surface chemistry, targeting ligands, and stimuli-responsive features. This review provides a comprehensive overview of the anatomy and physiology of the BBB, the key obstacles in CNS drug delivery, and the diverse classes of nanocarriers developed to enhance brain targeting, including polymeric nanoparticles, lipid-based systems, inorganic nanomaterials, biomimetic vectors, and hybrid multifunctional platforms. Advanced targeting strategies—such as receptor-mediated, carrier-mediated, and adsorptive-mediated transcytosis, along with focused ultrasound and intranasal delivery—are critically discussed for their therapeutic potential. We also examine pharmacokinetics, biodistribution, safety considerations, and the preclinical tools available for evaluating nanocarrier performance. Finally, we highlight ongoing challenges, regulatory constraints, and emerging trends such as AI-driven design, personalized neuro-nanomedicine, and next-generation BBB-on-chip systems. Together, these insights underscore the transformative potential of nanotechnology in shaping the future of neurotherapeutics.

Keywords:

Blood–Brain Barrier; CNS Drug Delivery; Nanocarriers; Neurotherapeutics; Receptor-Mediated Transcytosis; Biomimetic Nanoparticles; Lipid Nanoparticles; Nanomedicine.

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1. Introduction

Neurodegenerative and central nervous system (CNS) disorders—including Alzheimer's disease, Parkinson's disease, multiple sclerosis, and various forms of brain tumors—remain some of the most challenging conditions to treat due to the intrinsic complexity of the brain and its limited regenerative capacity. A major bottleneck in the effective management of these disorders is the blood–brain barrier (BBB), a highly specialized structural and biochemical interface that protects the brain from toxins, pathogens, and fluctuations in plasma composition [1-2]. While essential for maintaining neural homeostasis, this barrier severely restricts the entry of most therapeutic agents, with more than 98% of small molecules and nearly all biologics failing to reach therapeutic concentrations within the CNS. Conventional drug delivery systems often fall short in overcoming this barrier due to poor permeability, rapid systemic clearance, and off-target toxicity. In this landscape, pharmaceutical nanotechnology has emerged as a transformative strategy capable of enhancing drug transport across the BBB through mechanisms such as surface modification, receptor-mediated targeting, and controlled release. This review aims to provide a comprehensive understanding of BBB-targeted nanotechnological approaches, outlining their mechanistic basis, therapeutic potential, and translational relevance [3-4]. The scope encompasses the biological complexity of the BBB, design considerations for nano-based therapeutics, current preclinical and clinical progress, and prospects for overcoming neurological disease barriers. Figure 1

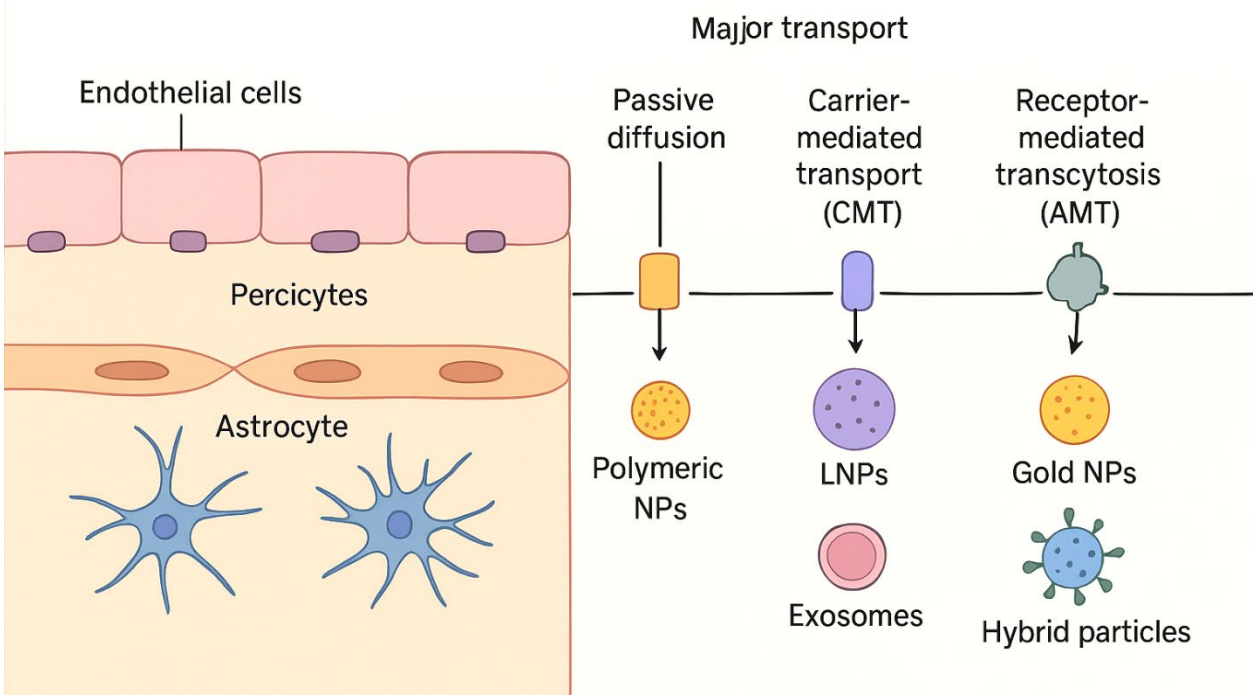

Figure 1: Schematic Overview of the Blood–Brain Barrier and Nanocarrier Entry Routes

2. Anatomy and Physiology of the Blood–Brain Barrier

The blood–brain barrier is formed by a dynamic multicellular neurovascular unit comprising brain microvascular endothelial cells, pericytes, astrocytic end-feet, and supporting basement membrane components. Endothelial cells serve as the structural backbone of the BBB, distinguished by minimal pinocytotic activity and the presence of tight junction proteins such as claudin-5, occludin, and

junctional adhesion molecules, which collectively maintain barrier integrity and restrict paracellular transport [5-6]. Pericytes regulate endothelial stability, angiogenesis, and permeability, while astrocytes modulate nutrient transport and reinforce the biochemical environment required for neuronal function. Multiple transport pathways coordinate the regulated movement of molecules across the BBB, including passive diffusion for lipophilic small molecules, carrier-mediated transport for glucose and amino acids, and receptor-mediated or adsorptive transcytosis for larger biomolecules. In pathological conditions such as Alzheimer's disease, Parkinson's disease, glioblastoma, and ischemic stroke, BBB integrity is compromised due to inflammation, oxidative stress, vascular dysfunction, and altered tight junction expression. Such disruptions can lead to impaired homeostasis but may also provide therapeutic windows for targeted drug delivery. Understanding these physiological and pathological mechanisms is crucial for the rational design of nanocarriers capable of safely and effectively navigating the BBB [6-7].

3. Barriers to CNS Drug Delivery

Delivering therapeutics to the central nervous system (CNS) is notoriously challenging due to the restrictive nature of the blood–brain barrier and the unique physiology of brain tissue. Only a very limited subset of small, lipophilic molecules can passively diffuse across the BBB, while large biologics—such as peptides, proteins, nucleic acids, and antibodies—are almost entirely excluded. Efflux transporters, including P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance-associated proteins (MRPs), further reduce drug accumulation by actively pumping xenobiotics back into the bloodstream. Even when therapeutic agents manage to cross the barrier, they often encounter enzymatic degradation by metabolic enzymes localized on endothelial cells or within the brain parenchyma [8-9]. Additional physiological constraints compound the challenge: the dense and highly structured brain extracellular matrix hinders drug diffusion, while the immune-privileged nature of the CNS limits inflammatory responses but also restricts immune-mediated therapeutic strategies. Together, these barriers underscore the need for advanced delivery platforms capable of improving penetration, retention, and therapeutic efficacy within the CNS [10].

4. Nanotechnology-Based Strategies for BBB Targeting

Nanotechnology has opened new frontiers in CNS therapeutics by enabling engineered platforms that can navigate, bypass, or actively exploit BBB transport pathways. These carriers offer tunable physicochemical properties, enhanced stability, targeted delivery, and controlled release, making them powerful tools for improving drug bioavailability in the brain [11].

4.1 Polymeric Nanoparticles

Polymeric nanoparticles—including PLGA-based systems, PEGylated carriers, and chitosan-derived nanostructures—are among the most widely explored platforms for CNS targeting. Their tunable degradation rates, high drug-loading capacity, and ability to protect sensitive therapeutics from enzymatic breakdown make them ideal for brain delivery. Surface functionalization with targeting ligands such as transferrin, lactoferrin, folate, peptides, or antibodies enables receptor-mediated transcytosis, significantly enhancing BBB penetration. These systems are especially useful for delivering hydrophobic drugs, nucleic acids, and neuroprotective agents [12].

4.2 Lipid-Based Nanocarriers

Lipid-based systems—including conventional liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs)—mimic biological membranes and offer excellent biocompatibility. Their ability to encapsulate both hydrophilic and lipophilic drugs makes them versatile for CNS applications. More recently, lipid nanoparticles (LNPs), popularized by mRNA vaccines, have been engineered to deliver RNA therapeutics across the BBB using ionizable lipids and targeted surface modifications. These platforms are particularly promising for gene silencing, gene editing, and protein replacement therapies in neurodegenerative diseases [13].

4.3 Inorganic Nanocarriers

Inorganic nanoparticles—including gold nanoparticles, mesoporous silica nanoparticles, and superparamagnetic iron oxide nanoparticles—offer unique properties such as optical responsiveness, magnetic maneuverability, and high surface area for drug loading. Their intrinsic imaging capabilities enable real-time tracking and theranostic applications, which are highly valuable in CNS disorders like glioblastoma. However, their clinical translation depends heavily on optimizing biodegradability and minimizing long-term toxicity, often achieved through advanced surface modifications [14].

4.4 Biomimetic and Cell-Derived Nanocarriers

Biomimetic nanocarriers leverage nature's own transport systems to improve BBB traversal. Exosomes—endogenous nanosized vesicles involved in intercellular communication—naturally cross the BBB and are being explored as carriers for siRNA, miRNA, and small molecules. Another emerging strategy uses cell membrane-coated nanoparticles, in which red blood cell, leukocyte, or platelet membranes provide immune evasion, prolonged circulation, and enhanced targeting to inflamed or diseased brain regions. These systems combine the advantages of synthetic nanotechnology with the biological sophistication of natural vesicles [15].

4.5 Hybrid Nanoplatforms

Hybrid nanocarriers integrate multiple materials—such as polymer–lipid combinations or metal–polymer architectures—to achieve complementary functionalities within a single platform. These multifunctional systems can simultaneously deliver drugs, genes, and imaging agents, facilitating both therapy and diagnosis (theranostics). Their modular design allows precise control over targeting, release kinetics, and BBB interaction mechanisms, making them highly adaptable for complex CNS conditions requiring combination therapy or real-time monitoring [16].

5. BBB Targeting Strategies

Overcoming the transport limitations of the blood–brain barrier requires strategic exploitation of its natural physiological pathways, and nanocarriers have been engineered to engage these routes with high precision. Receptor-mediated transcytosis (RMT) remains one of the most widely used approaches, leveraging receptors such as transferrin, lactoferrin, insulin, and low-density lipoprotein (LDL) to shuttle therapeutic-loaded nanoparticles across endothelial cells. Nanocarriers functionalized with monoclonal antibodies or ligand mimetics can bind these receptors with high affinity, enabling efficient and selective BBB penetration. Carrier-mediated transport (CMT) represents another targeted avenue, where nanoparticles are designed to interact with nutrient transporters—particularly glucose, amino acid, and peptide carriers—to hijack endogenous transport mechanisms for drug delivery [17-18]. Beyond

receptor-specific pathways, adsorptive-mediated transcytosis (AMT) exploits the electrostatic attraction between cationic nanoparticle surfaces and the negatively charged endothelial membrane, promoting nonspecific yet effective internalization. Physical methods further expand the BBB-targeting toolkit: focused ultrasound (FUS) enables temporary, localized BBB opening when used alongside microbubbles, while magnetic targeting utilizes iron oxide nanoparticles guided by external magnetic fields to accumulate therapeutics at precise brain regions. An alternative noninvasive route is intranasal nanocarrier delivery, which bypasses the BBB altogether by utilizing the olfactory and trigeminal pathways. Formulations incorporating mucoadhesive polymers significantly enhance retention and improve direct nose-to-brain transport, offering a patient-friendly strategy for CNS drug delivery [19-20].

6. Nanocarrier Applications in Neurotherapeutics

Nanotechnology continues to revolutionize CNS drug delivery by enabling disease-specific, targeted, and multifunctional therapeutic interventions. In Alzheimer's disease, nanocarriers are used to enhance the brain delivery of anti-amyloid agents, antioxidants, cholinesterase inhibitors, and emerging RNA-based therapeutics. Polymeric, lipid, and metal-based platforms have shown promise in reducing amyloid plaque burden, mitigating oxidative stress, and improving synaptic function. In Parkinson's disease, nanoparticles facilitate the sustained delivery of dopamine agonists, neuroprotective molecules, gene-silencing agents, and mitochondrial modulators, helping to address both motor and non-motor symptoms [21-22]. Glioblastoma, one of the most treatment-resistant brain tumors, benefits from targeted nanoplatforms that combine chemotherapy, photothermal therapy, immunomodulation, and imaging guidance to improve tumor specificity and reduce systemic toxicity. In stroke therapy, nanocarriers enable rapid delivery of thrombolytics, anti-inflammatory agents, neuroprotectants, and antioxidant therapies, supporting neuronal survival and functional recovery after ischemic or hemorrhagic injury. Across neurological disorders, nanotechnology also facilitates the delivery of complex biologics—including peptides, monoclonal antibodies, siRNA, miRNA, mRNA, and CRISPR components—by protecting these molecules from degradation and enhancing their penetration into deep brain regions. Collectively, these applications highlight the transformative potential of nanomedicine in reshaping treatment outcomes for diverse neurodegenerative and CNS diseases [23-24].

7. Pharmacokinetics, Biodistribution, and Safety

Understanding the pharmacokinetics and biodistribution of nanocarriers designed for CNS delivery is crucial, yet highly challenging due to the restrictive physiology of the blood–brain barrier. Traditional ADME paradigms often fail to accurately predict the behavior of nanosystems, as particle size, surface chemistry, charge, and protein corona formation significantly influence circulation time and BBB penetration. Tracking nanocarriers in vivo requires advanced analytical and imaging techniques, including fluorescence, MRI, PET, and radiolabeling approaches that allow real-time monitoring of their transport and accumulation within brain tissues. However, long-term toxicity remains a major concern—some nanomaterials may accumulate within the brain or peripheral organs, especially if they exhibit slow biodegradation rates, leading to potential neurotoxicity or systemic burden. Additionally, interactions between nanocarriers and the immune system can trigger unwanted responses such as microglial activation, cytokine release, and neuroinflammation, threatening both safety and therapeutic efficacy [25-26]. Addressing these pharmacokinetic and toxicological complexities is essential to ensure that CNS nanomedicine achieves clinical translation without compromising patient safety.

8. Preclinical Models and Evaluation Techniques

Rigorous preclinical evaluation is critical for assessing the therapeutic performance and safety of BBB-targeted nanocarriers, and this relies on a combination of in vitro and in vivo models. In vitro BBB systems, such as Transwell assays, co-culture models, and advanced microfluidic BBB-on-chip platforms, allow controlled assessment of permeability, transport mechanisms, and endothelial barrier integrity under physiologically relevant conditions. These models enable rapid screening but require confirmation in in vivo models, where rodents remain the most widely used due to their cost-effectiveness and well-characterized neurobiology [28-29]. Zebrafish models provide real-time optical transparency for studying nanoparticle biodistribution, while non-human primates offer the closest approximation to human BBB physiology for late-stage validation. To evaluate the CNS delivery efficiency and therapeutic impact of nanocarriers, researchers employ a range of imaging modalities—including MRI, PET, CT, and fluorescence imaging—to track nanoparticle localization and therapeutic payload distribution. Concurrently, the use of biomarkers and functional endpoints, such as cognitive performance, motor coordination, inflammatory markers, and neuronal survival indices, provides insight into both therapeutic efficacy and potential neurotoxicity. Together, these evaluation strategies create a comprehensive framework for advancing nanocarrier-based neurotherapeutics toward clinical readiness [30-31].

9. Challenges and Limitations

Despite remarkable progress in BBB-targeted nanomedicine, several challenges continue to limit clinical translation. One of the biggest barriers is the poor translatability of animal model data to humans, as rodent and even primate BBB physiology often fails to fully replicate human neurovascular complexity. This mismatch results in inconsistent therapeutic outcomes when moving from preclinical to clinical stages. Manufacturing poses another major obstacle: achieving scalable, reproducible, and GMP-compliant production of complex nanocarriers—especially multi-layered or biomimetic systems—remains technically demanding and costly [32-33]. Regulatory pathways further complicate development, as agencies require detailed characterization of nanoparticle composition, biodistribution, long-term safety, and degradation profiles, creating extensive approval timelines. Additionally, the heterogeneity of BBB permeability across patients and disease states introduces variability in therapeutic responses, making it difficult to establish standardized dosing strategies. These limitations highlight the need for better models, more robust manufacturing frameworks, and harmonized regulatory guidelines to unlock the full clinical potential of BBB-targeted nanotechnologies [34-35].

10. Future Perspectives

Looking ahead, the landscape of BBB-focused nanomedicine is poised for major transformation driven by innovations across nanotechnology, computational science, and bioengineering. AI-driven design is rapidly emerging as a powerful tool for predicting nanoparticle–BBB interactions, optimizing physicochemical properties, and accelerating lead candidate selection. The rise of personalized neuro-nanomedicine promises patient-specific formulations that account for individual differences in genetics, pathology, and BBB integrity [36-37]. Meanwhile, smart and stimuli-responsive nanocarriers capable of "on-demand" release—triggered by pH, enzymes, magnetic fields, or external energy sources—represent the next wave of precision CNS therapeutics. Advances in organ-on-chip and humanized BBB models offer unprecedented platforms for studying nanoparticle transport under physiologically relevant conditions, reducing reliance on animal studies. Furthermore, expanding theranostic

technologies will enable real-time monitoring of drug biodistribution, therapeutic response, and disease progression through integrated imaging capabilities. Collectively, these future directions pave the way toward more effective, safer, and customizable neurotherapeutic strategies [38-39].

11. Conclusion

BBB-targeted nanotechnology has emerged as one of the most promising frontiers in neurotherapeutics, offering novel solutions to longstanding challenges in delivering drugs to the central nervous system. Advances in polymeric, lipid-based, inorganic, biomimetic, and hybrid nanocarriers have demonstrated significant potential to enhance brain penetration, improve therapeutic efficacy, and enable multimodal treatment approaches. While hurdles related to translation, safety, manufacturing, and regulation remain, ongoing innovations—such as AI-guided design, next-generation BBB models, and adaptive nanoplatforms—are steadily closing the gap between laboratory research and clinical application. With continued multidisciplinary collaboration, nanotechnology is positioned to reshape the future of CNS medicine, paving the way for more precise, effective, and accessible treatments for neurodegenerative diseases, cancers, and other debilitating neurological disorders.

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