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Review Article

Nanocarriers for Brain Targeting: Overcoming the Blood-Brain Barrier in Neuropharmacology

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Abstract

The blood-brain barrier (BBB) is a highly selective physiological barrier that protects the central nervous system from harmful substances while maintaining brain homeostasis. However, the BBB significantly limits the delivery of therapeutic agents to the brain, creating major challenges in the treatment of neurological disorders. Conventional drug delivery systems often fail to achieve sufficient drug concentrations in brain tissues due to poor permeability, enzymatic degradation, and systemic elimination. Nanocarrier-based drug delivery systems have emerged as a promising strategy to overcome BBB-related limitations and improve targeted brain delivery. Nanocarriers such as liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles, nanoemulsions, metallic nanoparticles, and polymeric micelles offer enhanced drug stability, improved bioavailability, prolonged circulation time, controlled drug release, and targeted delivery to diseased brain tissues. These systems can cross the BBB through receptor-mediated transcytosis, adsorptive-mediated transcytosis, carrier-mediated transport, and temporary BBB modulation. Surface modification with ligands, peptides, antibodies, and polymers further enhances targeting efficiency and therapeutic outcomes. Nanocarrier-based approaches have shown promising applications in Alzheimer's disease, Parkinson's disease, epilepsy, stroke, multiple sclerosis, and brain tumours. Despite substantial progress, challenges related to toxicity, immunogenicity, scalability, regulatory approval, and long-term safety remain significant concerns. This review discusses the structure and functions of the BBB, mechanisms of nanocarrier transport across the BBB, different classes of nanocarriers, therapeutic applications in neuropharmacology, recent advancements, current limitations, and future perspectives in brain-targeted nanomedicine.

Keywords: Blood-brain barrier, Nanocarriers, Brain targeting, Neuropharmacology, Nanomedicine, Nanoparticles, Drug delivery systems.

Introduction

Neurological disorders are among the leading causes of disability and mortality worldwide[1]. Diseases such as Alzheimer's disease, Parkinson's disease, epilepsy, stroke, multiple sclerosis, Huntington's disease, brain tumours, and neuroinfections continue to present major therapeutic challenges[2]. One of the primary reasons for poor therapeutic success in treating central nervous system (CNS) disorders is the presence of the blood-brain barrier (BBB)[3], which acts as a protective interface between the bloodstream and the brain[4].

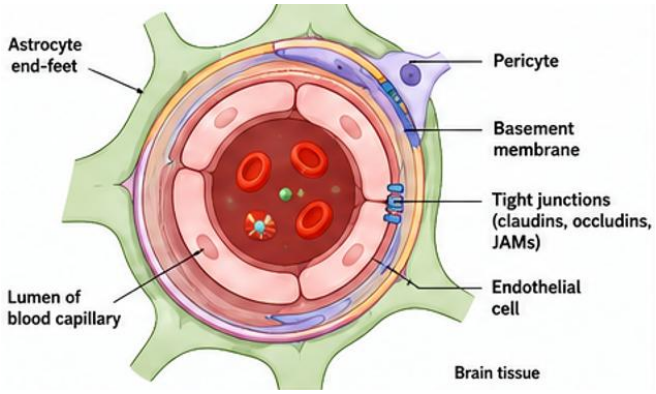


Figure 1: Structure of Blood Brain Barrier (BBB)

The BBB is composed of tightly connected endothelial cells, astrocytes, pericytes, basement membrane components, and neuronal cells that collectively regulate molecular transport into the brain[5]. Although the BBB protects the brain from toxins, pathogens, and harmful chemicals, it also restricts the entry of most therapeutic drugs. Studies indicate that approximately 98% of small-molecule drugs and almost all macromolecules are unable to effectively cross the BBB. As a result, conventional oral and intravenous formulations often fail to deliver adequate drug concentrations to the CNS[6].

The inability to efficiently transport drugs across the BBB has encouraged the development of advanced drug delivery systems. Among these, nanotechnology-based drug delivery systems have gained considerable importance in neuropharmacology. Nanocarriers are nanosized particles generally ranging from 1 to 1000 nm that can encapsulate therapeutic agents and transport them to targeted tissues[7]. Due to their small size, modifiable surface properties, high drug-loading capacity, and controlled release characteristics, nanocarriers have emerged as highly effective tools for brain-targeted drug delivery[8].

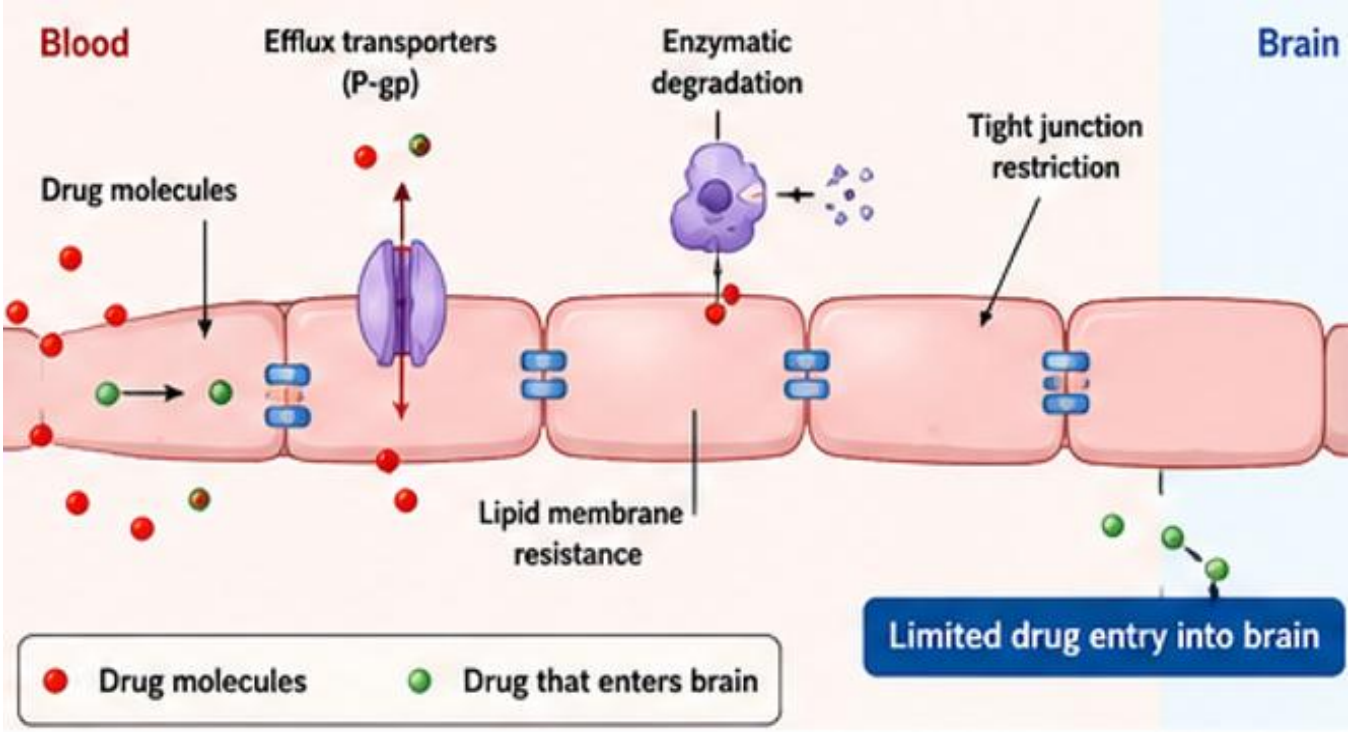


Figure 2: Challenges in conventional Drug Delivery Across BBB

Nanocarriers can improve drug solubility, reduce degradation, enhance pharmacokinetic properties, minimize systemic toxicity, and facilitate BBB penetration. Furthermore, the incorporation of targeting ligands, antibodies, peptides, surfactants, and polymers can significantly enhance selective drug accumulation within diseased brain regions. In recent years, substantial research efforts have focused on designing multifunctional nanocarriers capable of simultaneous diagnosis, imaging, and therapy.

This review provides a comprehensive overview of the BBB structure and functions, challenges in brain drug delivery, mechanisms of nanocarrier transport across the BBB, various types of nanocarriers used in neuropharmacology, therapeutic applications, advantages, limitations, and future opportunities in the field of brain-targeted nanomedicine.

Components of the Blood-Brain Barrier (BBB)

The blood-brain barrier (BBB) is a highly selective and protective physiological barrier that separates the central nervous system (CNS) from systemic circulation. It is mainly composed of brain capillary endothelial cells, tight junctions, astrocytes, pericytes, and the basement membrane, which together form the neurovascular unit. Brain capillary endothelial cells are tightly connected through specialized tight junction proteins such as claudins, occludins, and junctional adhesion molecules[9]. These tight junctions restrict paracellular diffusion and maintain the structural integrity of the BBB. Tight junctions specifically prevent the free movement of hydrophilic molecules between endothelial cells, thereby contributing to the low permeability of the barrier. Astrocytes play a major supportive role through their end-feet that surround the brain capillaries and regulate BBB permeability, nutrient transport, and ionic balance. Pericytes, embedded within the basement membrane, contribute to vascular stability, angiogenesis, and maintenance of BBB function. The basement membrane itself provides structural support and regulates cellular interactions within the neurovascular unit[10].

Table 1: Components of the Blood-Brain Barrier (BBB)

Component	Structure	Function
Brain capillary endothelial cells	Tightly packed endothelial cells with tight junctions	Primary physical barrier controlling transport
Tight junctions (claudins, occludins, JAMs)	Protein complexes between endothelial cells	Restrict paracellular diffusion
Astrocytes	Glial cells with end-feet surrounding capillaries	Regulate BBB permeability and support neurons
Pericytes	Embedded in basement membrane	Maintain vascular stability and BBB integrity
Basement membrane	Extracellular matrix layer	Structural support and cell signalling regulation

Functions of the BBB

The BBB performs several essential physiological functions necessary for maintaining brain homeostasis[11]. It protects the brain from harmful toxins, pathogens, and circulating xenobiotics while selectively allowing the entry of nutrients and essential molecules. The BBB regulates nutrient transport, maintains ionic balance, and prevents neuroinflammation by restricting immune cell infiltration[12]. It also controls neurotransmitter balance within the CNS, thereby ensuring proper neuronal signalling and brain function[13].

Challenges in Drug Delivery Across the BBB

Despite its protective role, the BBB presents a major challenge in the delivery of therapeutic agents to the brain[14]. Tight junctions significantly restrict paracellular transport, limiting the entry of many drugs. Efflux transporters such as P-glycoprotein actively expel therapeutic compounds from endothelial cells back into systemic circulation, thereby reducing drug accumulation in the brain. Enzymatic degradation within the BBB further decreases drug stability and therapeutic efficacy[15]. Additionally, drugs with large molecular size exhibit poor permeability across the BBB, while hydrophilic compounds generally show limited penetration due to their inability to diffuse through the lipid-rich endothelial membranes. These barriers greatly reduce the effectiveness of conventional neurotherapeutic agents[16].

Nanocarriers in Brain Drug Delivery

Nanocarriers are nanoscale delivery systems specifically designed to transport drugs, proteins, genes, or imaging agents to targeted tissues, including the brain. Due to their unique physicochemical properties, nanocarriers can improve BBB penetration and enhance targeted delivery to CNS tissues[17]. These systems offer several advantages such as enhanced drug solubility, improved stability, controlled and sustained drug release, increased bioavailability, reduced systemic toxicity, and protection of drugs from enzymatic degradation. Furthermore, nanocarriers improve therapeutic efficacy through targeted drug delivery and enhanced BBB permeability[18].

Types of Nanocarriers for Brain Targeting

Liposomes are spherical vesicular systems composed of phospholipid bilayers surrounding an aqueous core. They can encapsulate both hydrophilic and lipophilic drugs and are widely used because of their biocompatibility, biodegradability, low toxicity, and controlled drug release properties[19]. Surface modifications using polyethylene glycol (PEG), transferrin, lactoferrin, or apolipoproteins improve BBB penetration through receptor-mediated transport mechanisms. Liposomal formulations have been investigated for the treatment of Alzheimer's disease, Parkinson's disease, brain tumours, and glioblastoma.

Polymeric nanoparticles are colloidal systems prepared using biodegradable polymers such as PLGA, chitosan, polycaprolactone, and PEG. These nanoparticles provide controlled drug release, improved stability, prolonged circulation time, and easy surface modification. They have been widely investigated for delivering anticancer drugs, antioxidants, peptides, proteins, and neuroprotective agents. Chitosan nanoparticles are particularly valuable due to their mucoadhesive properties and ability to enhance nasal brain delivery[20].

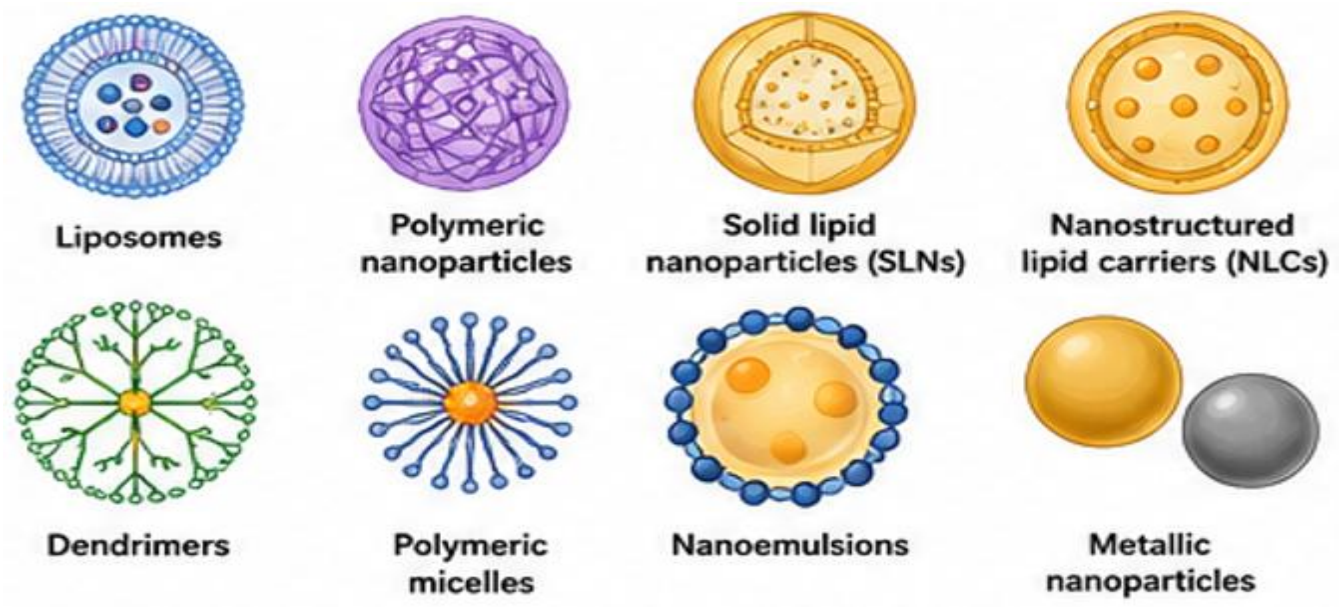


Figure 3: Types Of Nanocarriers for Brain Targeting

Solid lipid nanoparticles (SLNs) consist of solid lipid cores stabilized by surfactants and offer advantages including high physical stability, controlled release, low toxicity, and improved drug protection. SLNs have been explored for the treatment of Alzheimer's disease, Parkinson's disease, and epilepsy. Nanostructured lipid carriers (NLCs), considered second-generation lipid nanoparticles, contain both solid and liquid lipids, allowing higher drug loading, improved stability, reduced drug leakage, and enhanced bioavailability. NLCs are especially promising for nose-to-brain delivery systems[21].

Dendrimers are highly branched polymeric nanostructures with a well-defined architecture and multiple surface functional groups[22]. Their controlled molecular structure and high drug-loading capacity make them useful for gene therapy, brain tumour targeting, and delivery of anti-inflammatory agents.

Polymeric micelles are self-assembled colloidal structures formed from amphiphilic polymers that can solubilize hydrophobic drugs and improve circulation time. They are commonly used in anticancer therapy and for delivering poorly soluble CNS drugs[23].

Nanoemulsions are thermodynamically stable dispersions of oil and water that enhance drug absorption, BBB permeability, and non-invasive administration. Intranasal nanoemulsions can bypass the BBB through the olfactory and trigeminal nerve pathways, providing direct brain targeting. Metallic nanoparticles such as gold, silver, and iron oxide nanoparticles possess unique imaging, magnetic targeting, and photothermal therapy capabilities. These nanoparticles are investigated for brain tumour imaging, targeted chemotherapy, and diagnostic imaging applications[24].

Table 2: Major Types of Nanocarriers for Brain Targeting

Nanocarrier	Composition	Key Features	Applications
Liposomes	Phospholipid bilayers	Biocompatible, dual drug loading	Alzheimer's, brain tumours
Polymeric nanoparticles	PLGA, chitosan, PEG	Controlled release, stable	Neuroprotection, anticancer drugs
Solid lipid nanoparticles (SLNs)	Solid lipid core	Low toxicity, sustained release	Alzheimer's, epilepsy
Nanostructured lipid carriers (NLCs)	Solid + liquid lipids	High drug loading, stability	Nose-to-brain delivery
Dendrimers	Branched polymers	High surface functionality	Gene therapy, brain tumours
Polymeric micelles	Amphiphilic polymers	Solubilize hydrophobic drugs	CNS anticancer therapy
Nanoemulsions	Oil-water system	High absorption, intranasal delivery	CNS drug delivery

Mechanisms of BBB Transport by Nanocarriers

Nanocarriers cross the BBB through several transport mechanisms. Receptor-mediated transcytosis involves the functionalization of nanocarriers with ligands that bind to receptors such as transferrin, insulin, and LDL receptors on endothelial cells[25].

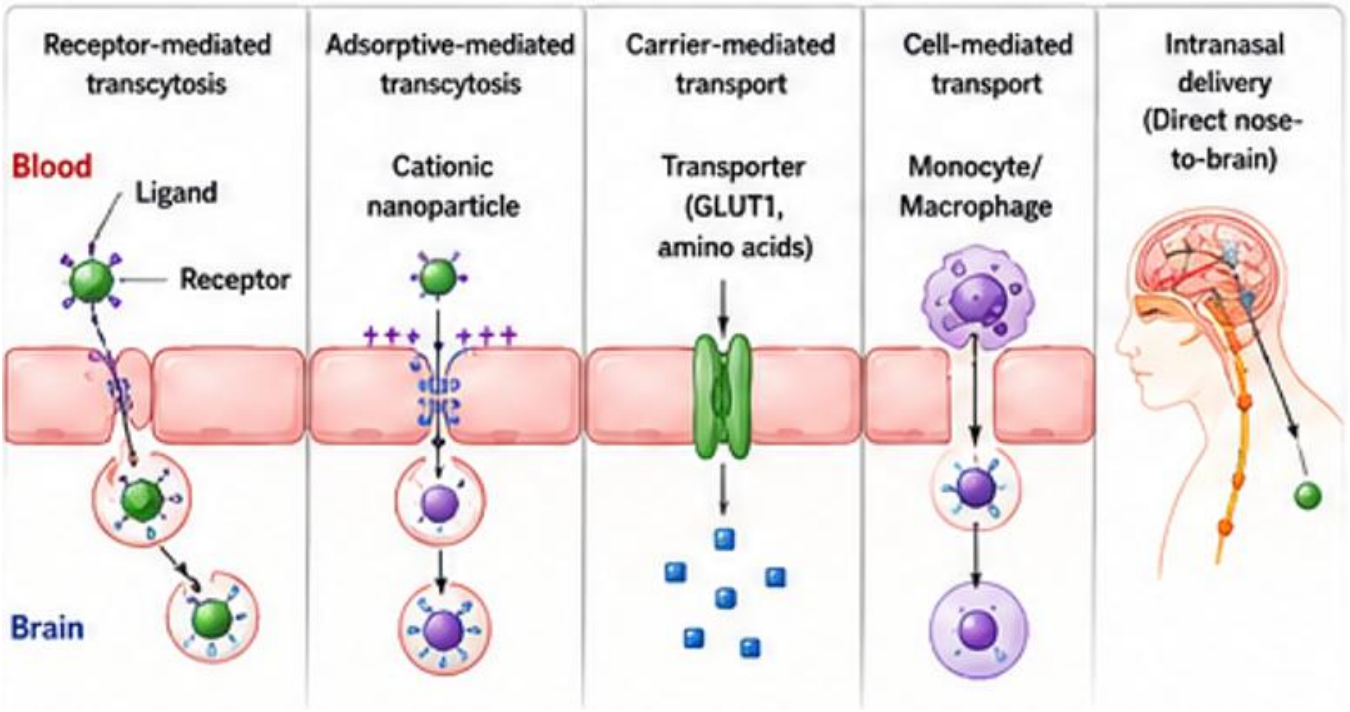


Figure 4: Mechanisms Of BBB Transport of Nanocarriers

This interaction initiates endocytosis and subsequent transport into the brain. Adsorptive-mediated transcytosis occurs through electrostatic interactions between positively charged nanocarriers and negatively charged endothelial membranes, facilitating cellular uptake. Carrier-mediated transport utilizes endogenous nutrient transporters such as glucose or amino acid transporters for drug delivery across the BBB. In cell-mediated transport, immune cells such as macrophages carry nanoparticles across the BBB into inflamed brain tissues.

Table 3: Mechanisms of BBB Transport for Nanocarriers

Mechanism	Description	Example
Receptor-mediated transcytosis	Ligand binding to BBB receptors triggers endocytosis	Transferrin, insulin receptors
Adsorptive-mediated transcytosis	Electrostatic interaction with endothelial cells	Cationic nanoparticles
Carrier-mediated transport	Uses nutrient transporters	Glucose transporter (GLUT1)
Cell-mediated transport	Immune cells carry nanoparticles	Macrophage-mediated delivery
Nasal route bypass	Direct brain entry via olfactory pathway	Nanoemulsions, SLNs

Surface Modification Strategies

Surface engineering strategies significantly improve brain-targeting efficiency and circulation stability of nanocarriers. PEGylation, or PEG coating, increases circulation time, reduces immune clearance, and enhances nanoparticle stability. Ligand conjugation improves receptor-specific targeting through molecules such as transferrin, lactoferrin, folic acid, and ApoE peptides. Antibody functionalization using monoclonal antibodies further enhances selective BBB transport and disease-specific targeting[26].

Table 4: Surface Modification Strategies for Brain Targeting

Strategy	Purpose	Example	Outcome
PEGylation	Increase circulation time	PEG-coated liposomes	Reduced immune clearance
Ligand conjugation	Target receptor binding	Transferrin, folic acid	Enhanced BBB penetration
Antibody functionalization	Disease-specific targeting	Monoclonal antibodies	High selectivity
Surfactant coating	Improve permeability	Polysorbate 80	Better brain uptake
Peptide modification	Target neuronal receptors	ApoE peptides	Improved CNS delivery

Applications in Neuropharmacology

Nanocarrier-based drug delivery systems have shown promising applications in neuropharmacology. In Alzheimer's disease, nanocarriers improve the delivery of donepezil, curcumin, rivastigmine, and anti-amyloid agents, thereby reducing amyloid plaque formation and oxidative stress[27]. In Parkinson's disease, nanoparticles enhance the delivery of dopamine and levodopa, improving motor function and reducing adverse effects. For brain tumours, nanocarriers enable selective drug accumulation within tumour tissues while minimizing systemic toxicity[28].

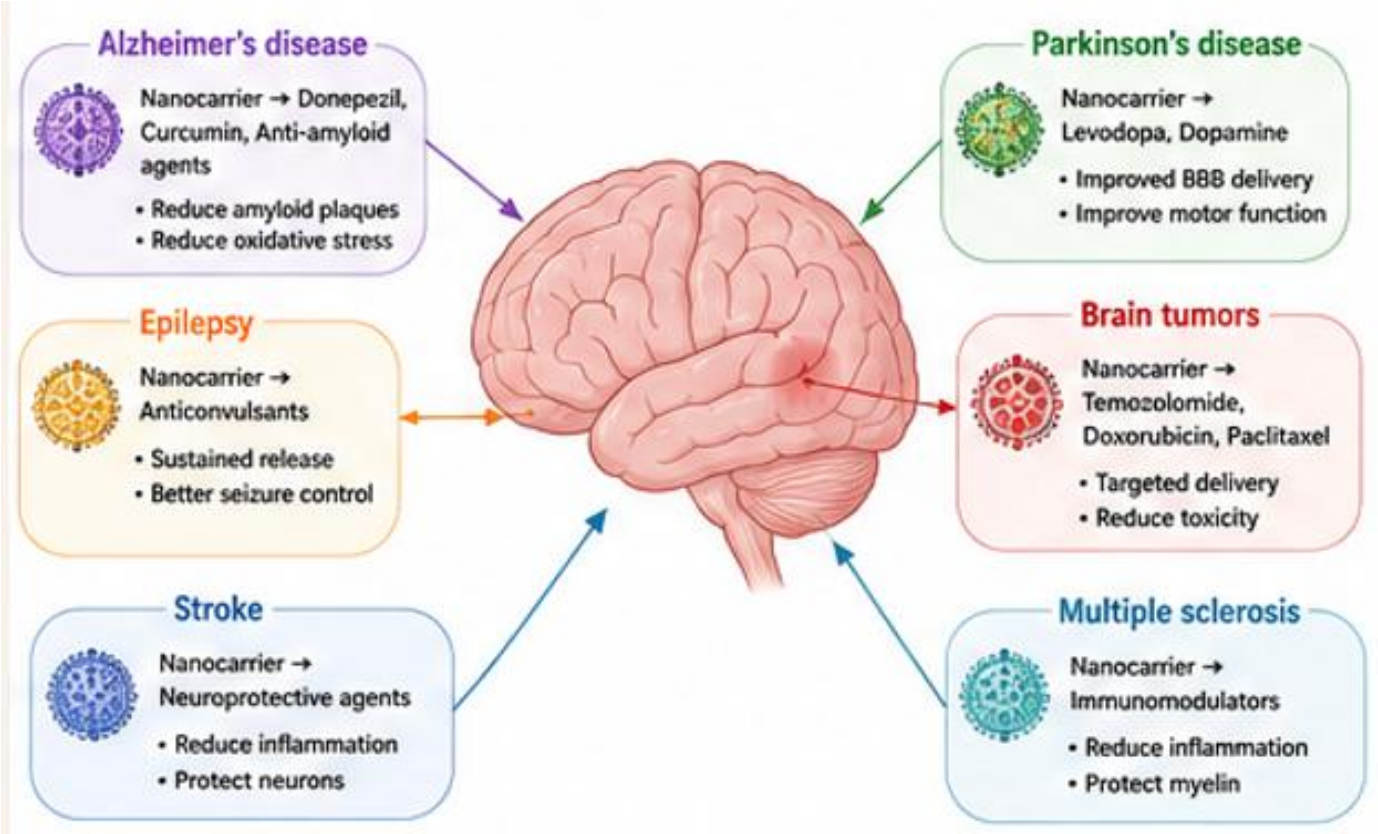


Figure 5: Nanocarriers Applications in Neurological Disorders

Drugs such as temozolomide, doxorubicin, and paclitaxel have been successfully investigated using nanocarrier systems. Nanocarriers also improve anticonvulsant delivery in epilepsy and reduce drug resistance. In stroke therapy, neuroprotective nanocarriers help reduce inflammation, oxidative stress, and neuronal damage after ischemic injury. In multiple sclerosis, nanocarriers facilitate the delivery of anti-inflammatory and immunomodulatory agents to affected CNS tissues[29].

Table 5: Therapeutic Applications of Nanocarriers in CNS Disorders

Disease	Therapeutic Agents	Role of Nanocarriers	Outcome
Alzheimer's disease	Donepezil, curcumin	Amyloid targeting, antioxidant delivery	Reduced plaque formation
Parkinson's disease	Levodopa, dopamine	Enhanced BBB penetration	Improved motor function
Brain tumours	Temozolomide, doxorubicin	Targeted chemotherapy	Reduced systemic toxicity
Epilepsy	Anticonvulsants	Sustained drug release	Improved seizure control
Stroke	Neuroprotective agents	Anti-inflammatory delivery	Reduced neuronal damage
Multiple sclerosis	Immunomodulators	CNS-specific delivery	Reduced inflammation

Toxicity and Safety Concerns

Although nanocarriers offer numerous therapeutic benefits, they may also produce adverse effects such as cytotoxicity, oxidative stress, neuroinflammation, immunogenicity, and accumulation within organs[30]. Long-term safety studies and detailed toxicological evaluations are essential before the successful clinical translation of nanomedicine-based therapies[31].

Regulatory Challenges

The development of brain-targeted nanomedicine faces several regulatory challenges, including the standardization of characterization methods, reproducibility, scale-up manufacturing, stability testing, and clinical trial requirements. Regulatory agencies worldwide continue to develop comprehensive guidelines for the approval and commercialization of nanomedicine products[32].

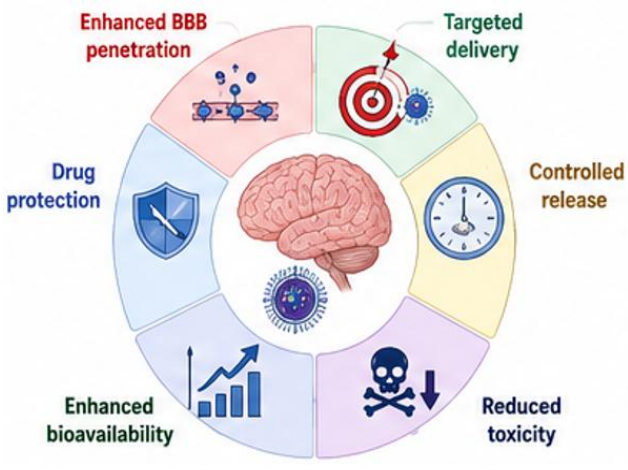


Figure 6: Graphical Presentations - Neurological Disorders

Recent Advances in Brain-Targeted Nanomedicine

Recent advancements in brain-targeted nanomedicine include the development of stimuli-responsive nanoparticles, magnetic targeting systems, gene-loaded nanoparticles, CRISPR-based nanocarriers, theranostic nanoparticles, and artificial intelligence-assisted nanocarrier design. These innovative technologies hold significant potential for revolutionizing neuropharmacological therapies and improving treatment outcomes[33].

Future Perspectives

Future research in brain-targeted nanomedicine should focus on the development of personalized nanomedicine approaches, safer biodegradable materials, multifunctional targeting systems, large-scale manufacturing processes, and long-term toxicity evaluation[34]. The integration of nanotechnology with artificial intelligence, precision medicine, and molecular diagnostics is expected to greatly improve the efficacy and safety of future neurotherapeutic strategies[35].

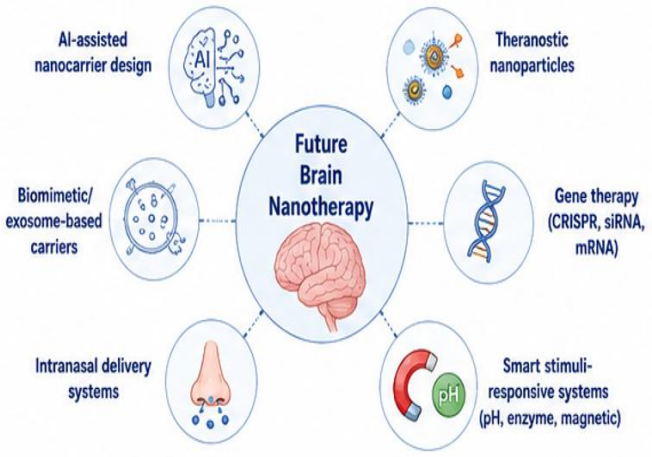


Figure 7: Graphical Presentations - Future Directions in Brain Nanomedicine

In the coming years, advanced nanocarrier systems capable of simultaneous diagnosis, imaging, targeted therapy, and real-time monitoring are expected to play a major role in the treatment of neurological disorders[36]. Theranostic nanocarriers combining therapeutic and diagnostic functions may enable early disease detection and personalized treatment planning[37]. The application of artificial intelligence and machine learning in nanomedicine design can further optimize nanoparticle

composition, predict BBB permeability, improve targeting efficiency, and accelerate formulation development[38].

Gene-editing technologies such as CRISPR-Cas systems incorporated into nanocarriers may provide new therapeutic opportunities for genetic and neurodegenerative disorders. Similarly, RNA-based therapeutics, including siRNA, mRNA, and microRNA delivery using nanocarriers, are gaining increasing attention for their potential in regulating disease-related genes within the CNS[39]. Stimuli-responsive or "smart" nanoparticles that respond to pH, temperature, magnetic fields, enzymes, or oxidative stress may also improve site-specific drug release and reduce systemic toxicity[40].

Intranasal and non-invasive brain delivery approaches are expected to become more important in future neuropharmacology due to their ability to bypass the BBB and improve patient compliance[41]. Additionally, the development of biomimetic nanoparticles, exosome-based delivery systems, and cell membrane-coated nanocarriers may further enhance biocompatibility, immune evasion, and targeted brain delivery[42].

Another important future direction involves improving the clinical translation of nanomedicines through standardized characterization methods, scalable manufacturing techniques, reproducible quality control systems, and harmonized international regulatory guidelines[43]. Greater collaboration among pharmaceutical scientists, clinicians, nanotechnologists, regulatory agencies, and industry partners will be essential for successful commercialization[44].

Furthermore, long-term in vivo safety studies, pharmacokinetic evaluations, biodistribution analysis, and toxicity assessments must be prioritized to ensure the safe clinical application of nanocarrier systems. Ethical considerations, environmental impact, and cost-effectiveness should also be addressed to facilitate broader accessibility and acceptance of nanomedicine-based therapies.

Overall, the future of brain-targeted nanomedicine is highly promising. Continued advancements in nanotechnology, biotechnology, neuroscience, and computational sciences are expected to revolutionize neuropharmacology and provide safer, more efficient, and highly targeted therapeutic strategies for the management of complex neurological disorders.

Conclusion

Nanocarrier-based drug delivery systems have emerged as a highly promising approach for overcoming the challenges associated with the blood-brain barrier in neuropharmacology. The BBB, while essential for protecting the brain and maintaining neural homeostasis, significantly restricts the entry of therapeutic agents into the central nervous system, thereby limiting the effectiveness of conventional treatments for neurological disorders. Advances in nanotechnology have enabled the development of multifunctional nanocarriers capable of improving drug solubility, enhancing bioavailability, prolonging circulation time, protecting drugs from enzymatic degradation, and facilitating targeted delivery to diseased brain tissues.

Various nanocarrier systems, including liposomes, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, dendrimers, nanoemulsions, metallic nanoparticles, and polymeric micelles, have demonstrated substantial potential in crossing the BBB through mechanisms such as receptor-mediated transcytosis, adsorptive-mediated transport, carrier-mediated transport, and cell-mediated delivery. Surface modification strategies involving PEGylation, ligand conjugation, and antibody functionalization have further improved targeting specificity and therapeutic efficiency.

Nanocarrier-based therapies have shown encouraging results in the management of Alzheimer's disease, Parkinson's disease, epilepsy, stroke, multiple sclerosis, and brain tumours. In addition to therapeutic applications, recent innovations such as theranostic nanoparticles, gene-loaded nanocarriers, CRISPR-based systems, and AI-assisted nanocarrier design represent significant advancements in precision neuropharmacology.

Despite these promising developments, several challenges remain unresolved, including toxicity, immunogenicity, long-term safety concerns, large-scale manufacturing difficulties, reproducibility issues, and regulatory complexities. Therefore, extensive preclinical and clinical investigations are still required to ensure the safety, efficacy, and successful translation of nanocarrier systems into clinical practice.

Overall, nanocarrier-mediated brain targeting represents a transformative strategy in modern neuropharmacology. Continued interdisciplinary research integrating nanotechnology, biotechnology, artificial intelligence, and precision medicine is expected to accelerate the development of safer and more effective brain-targeted therapies, ultimately improving the treatment and quality of life of patients suffering from neurological disorders.

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