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Brain Drug Delivery- An Updated Review Article for Mechanism and Recent Technologies

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Abstract

Background: Effective brain drug delivery remains a significant challenge due to the restrictive nature of the blood-brain barrier (BBB). This review article examines the mechanisms and recent advancements in brain drug delivery systems, addressing the challenges and factors influencing successful therapeutic interventions.

Objective: To provide a comprehensive overview of current technologies and strategies for enhancing drug delivery to the brain, with a focus on nasal-to-brain delivery systems.

Methods: We analysed recent literature on various drug delivery systems, including nanoparticle-based formulations, liposomal technologies, and chemical permeation enhancers. We also evaluated the impact of factors such as drug properties, formulation characteristics, and physiological conditions on delivery efficacy.

Results: Advances in drug delivery systems have demonstrated significant progress in overcoming the BBB. Nanoparticle-based systems and liposomal formulations have shown enhanced permeability and targeted delivery capabilities. The nasal-to-brain route has emerged as a promising non-invasive strategy, utilizing the olfactory and trigeminal nerve pathways to facilitate direct access to the central nervous system. Formulations utilizing mucoadhesive polymers have improved drug solubility, stability, and residence time in the nasal cavity, leading to increased therapeutic effectiveness.

Conclusion: Understanding the mechanisms influencing brain drug delivery is crucial for developing effective treatments for neurological disorders. This review highlights the critical advancements in delivery systems, emphasizing the need for ongoing research to optimize strategies that enhance drug penetration across the BBB. Future studies should focus on refining these technologies to improve patient outcomes and address the growing burden of central nervous system diseases.

Keywords: brain drug delivery, blood-brain barrier (BBB), nanoparticles, liposomal formulations, nasal-to-brain delivery, central nervous system (CNS), drug permeability, therapeutic efficacy, mucoadhesive polymers, neurological disorders..

1. Introduction

Neurological disorders, including central nervous system (CNS) conditions and brain tumors, represent some of the most common and devastating illnesses, yet they remain inadequately addressed therapeutically. The global landscape for drug development targeting brain diseases must expand significantly over the next two decades, given the rising populations of elderly individuals and those suffering from CNS disorders. Nonetheless, drug development in this domain experiences the lowest success rates when compared to other therapeutic fields. The timeline for creating CNS pharmaceuticals typically exceeds that of non-CNS medications.

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Conducting clinical trials for CNS drugs is particularly challenging due to the intricacies of brain function, potential adverse effects, and the restrictive nature of the blood-brain barrier (BBB) (1). Furthermore, the absence of effective technologies for facilitating drug transport across the BBB presents a significant obstacle to CNS drug development. Both small molecules and macromolecules are being explored as potential therapeutic agents for a variety of brain disorders (2). However, only small molecules that are lipid-soluble and possess a molecular weight of less than 400 Da can traverse the BBB, as most macromolecules are unable to penetrate the brain's endothelial barrier. This physiological limitation posed by the BBB effectively excludes 95% of compounds from drug development pipelines. Recent research indicates that the BBB functions as a dynamic interface regulating the passage of substances from the bloodstream into the brain (3). These findings highlight the necessity of reassessing certain paradigms surrounding brain drug delivery and unveil substantial opportunities for novel strategies aimed at administering drugs to the brain.

The Blood-Brain Barrier:

In order to preserve homeostasis and prevent different substances from the bloodstream from entering the brain, the blood-brain barrier (BBB) acts as a crucial diffusion barrier required for the brain's regular operation. Tight junctions (TJs), neurons, pericytes, astrocytes, brain microvascular endothelial cells (ECs), and the basal membrane make up the BBB, which is made up of closely packed brain capillaries (4, 5). The absence of fenestrations in these brain capillary ECs limits the transport of proteins and small molecules. The ECs are joined by interendothelial junctions to create a continuous barrier that severely restricts the passage of chemicals that dissolve in water. The impermeable BBB is formed by the basal membrane, astrocytes, pericytes, and ECs surrounding them. Further preventing chemicals from entering the brain are efflux transporters found in brain capillary ECs. Interendothelial junctions, which are made up of protein complexes such adherens junctions, TJs, and gap junctions, are mostly responsible for controlling the BBB's permeability (6). TJs are essential for preserving the permeability barrier of both epithelial and endothelial cells, which in turn regulates tissue homeostasis, whereas adherens junctions are critical for controlling the permeability of the endothelial barrier (7). Gap junctions, which are made up of six connexin molecules, allow ECs to communicate chemically and electrically (5). Instead of having a fixed structure, the BBB's constituent parts are constantly adapting to different physiological changes that take place in the brain (3,6).

Either a transcellular (across the cells) or paracellular (between nearby cells) pathway allows molecules to pass through the blood-brain barrier. Ions and solutes can use concentration gradients for passive diffusion across the blood-brain barrier thanks to the paracellular route. The transcellular pathway, on the other hand, includes a number of processes, such as transcytosis, receptor-mediated transport, and passive diffusion. A non-saturable process that depends on the molecules' physicochemical properties is passive diffusion. Molecular weight, charge, lipid solubility, surface activity, and relative molecular size are all factors that affect BBB permeability (2). For example, the transcellular channel allows for the passive diffusion of tiny lipophilic substances, such as carbon dioxide, across the blood-brain barrier. Moreover, enzymatic activity, cerebral blood flow, plasma protein binding, efflux transporters (e.g., P-glycoprotein (P-gp)), and other physiological variables may influence BBB permeability (8). Certain and saturable receptor-mediated transport systems, such as glucose transporter-1 (GLUT-1), insulin transporter, and transferrin transporter, allow hydrophilic molecules, like proteins and peptides, to enter the brain (9). Both the luminal and abluminal membranes of ECs exhibit these endogenous transporters. Receptor-mediated transcytosis has attracted a lot of interest among the several transport systems because of its potential to carry medications into the brain (10). Innovative approaches to drug administration to the brain will be facilitated by a thorough understanding of the mechanisms controlling transit across the blood-brain barrier.

Blood-Brain Barrier Disruption in Specific Pathological Conditions

The blood-brain barrier (BBB) undergoes disruption in various pathological conditions associated with diseases such as stroke, diabetes, seizures, hypertensive encephalopathy, acquired immunodeficiency syndrome, traumatic brain injuries, multiple sclerosis, Parkinson's disease (PD), and Alzheimer's disease (AD) (11). In these pathological states, the remodeling of protein complexes within interendothelial junctions plays a crucial role in the breakdown of the BBB (6). For instance, during ischemic stroke, the BBB exhibits hyper-permeability to macromolecules. Shiraishi et al. conducted a comparison of Gadolinium micelles (Gd-micelles) and Gd-DTPA magnetic resonance imaging (MRI) contrast agents in rats following intravenous injection. Their findings revealed a significantly stronger contrast signal from Gd-micelles in the ischemic hemisphere compared to Gd-DTPA, indicating a hyper-permeable BBB under ischemic conditions (12). Albumin, a large protein molecule, serves as a marker for studying BBB leakage due to its limited ability to cross a healthy BBB. FITC-albumin was detected in the brain at both early and late stages of Huntington's disease in an R6/2 mouse model, signifying BBB disruption in these instances (13). In multiple sclerosis, the disorganization of junctional molecules within cholesterol-rich regions of cell membranes contributes to increased BBB permeability

(7). Additionally, the integrity of adherens junctions can be substantially affected, further altering BBB permeability (14). It has been established that junctional disruptions result in a permeable BBB in certain diseases. However, the extent and timeline of BBB disruption in each condition remain inadequately characterized due to various limitations. For example, both transient and chronic loss of BBB integrity is consistently observed in multiple sclerosis. While BBB disruption can be visualized in vivo through the injection of Gd contrast agents, MRI scans may not fully represent the overall scope of BBB compromise. Moreover, BBB disruption is often linked to disease complications. In the context of AD, vascular dementia and AD frequently coexist. Despite the presence of conflicting data, there is a consensus that increased BBB permeability in some AD patients is attributed to vascular dementia rather than occurring in pure AD alone (15). Given the complexity of processes involved in CNS diseases, research on BBB disruption across various disorders remains in a relatively rudimentary state to date.

Blood-Brain Tumor Barrier

Gliomas represent the most prevalent category of primary brain tumors. In their initial stages, brain tumor cells mimic the characteristics of the blood-brain barrier (BBB) to accommodate their rapid proliferation and migration. However, as tumor cells reach a certain threshold, the integrity of the BBB becomes compromised, resulting in the formation of the blood-brain tumor barrier (BBTB), which consists of newly formed blood vessels (brain tumor capillaries) and differs from the BBB. The permeability of the BBTB in glioblastomas is notably high in the core tumor regions, while it is significantly lower or absent in peripheral areas (16). Consequently, the combination of the BBB and the BBTB creates a formidable obstacle for the delivery of therapeutics to brain tumors. Strategies employed to surmount the BBB, such as utilizing hyperosmotic solutions of mannitol or compounds like bradykinin to open tight junctions, inhibiting efflux drug transporters, and employing receptor-mediated drug delivery systems, can also be adapted to selectively enhance drug delivery to brain tumors. Additionally, effective targeting of glioma cells is essential for successful treatment. One approach involves coating nanoparticles with cell-permeable peptides to facilitate this targeting. A comprehensive review detailing peptides designed for targeting glioma cells can be found (17), with a primary emphasis on the mechanisms for crossing the BBTB.

Factors and Challenges Facing Brain Delivery:

The delivery of therapeutics to the brain is fraught with significant challenges due to the intricate physiology of the central nervous system (CNS) and the presence of the blood-brain barrier (BBB). This barrier, while essential for maintaining the brain's microenvironment, poses a formidable obstacle for drug delivery. Several key factors contribute to the challenges associated with brain delivery, including the physicochemical properties of drugs, the dynamic nature of the BBB, and the specific characteristics of brain tumors, which create a unique blood-brain tumor barrier (BBTB).

Physicochemical Properties of Drugs

One of the foremost challenges in brain drug delivery is the physicochemical properties of therapeutic agents. The BBB is highly selective, permitting the passage of only certain molecules based on their size, charge, and lipid solubility. Typically, small, lipophilic molecules with a molecular weight of less than 400 Da can cross the BBB effectively; however, most therapeutic macromolecules, including proteins and peptides, are unable to penetrate due to their size and hydrophilicity. This inherent limitation necessitates the design of drugs that possess optimal characteristics for BBB penetration. For instance, enhancing lipophilicity or modifying molecular structures to improve transport across the BBB may facilitate drug delivery. Additionally, the influence of molecular weight, surface activity, and charge cannot be overlooked, as these physicochemical factors significantly impact the permeability of the BBB and, consequently, the efficacy of CNS therapies.

Dynamic Nature of the Blood-Brain Barrier

The dynamic nature of the BBB further complicates drug delivery. The BBB is not a static structure; its permeability can vary based on numerous physiological and pathological conditions. For instance, in certain neurological disorders, such as multiple sclerosis or Alzheimer's disease, the BBB may exhibit increased permeability, allowing larger molecules to cross. Conversely, in healthy individuals, the BBB maintains a tight control over substance entry, effectively restricting many therapeutic agents. Understanding the mechanisms regulating BBB permeability, including the role of tight junctions and transporters, is essential for developing strategies to enhance drug delivery. Techniques such as receptor-mediated transport and the use of efflux pump inhibitors are being explored to exploit the BBB's transport mechanisms. Furthermore, advances in nanotechnology, such as the use of nanoparticles and liposomes, hold promise for overcoming BBB challenges by improving drug solubility, stability, and targeted delivery.

Blood-Brain Tumor Barrier Considerations

In the context of brain tumors, particularly glioblastomas, the situation becomes even more complex due to the presence of the blood-brain tumor barrier (BBTB). This barrier arises as a result of tumor angiogenesis, leading to the formation of abnormal blood vessels that exhibit different permeability characteristics compared to the BBB. The BBTB often demonstrates high permeability in tumor core regions, which can facilitate drug delivery; however, its properties can also lead to increased efflux of therapeutic agents, thereby limiting their effectiveness. Additionally, the heterogeneity of tumor

microenvironments and the presence of a cancer stem cell population further complicate targeted drug delivery. To enhance drug uptake, novel strategies such as the use of cell-penetrating peptides and targeted nanoparticle formulations are being developed. These approaches aim to facilitate the selective targeting of glioma cells while minimizing off-target effects.

Regulatory and Manufacturing Challenges

Beyond the physiological barriers, regulatory and manufacturing challenges also pose significant hurdles for brain delivery. The development of drugs specifically designed to cross the BBB requires extensive preclinical and clinical testing to ensure their safety and efficacy. Regulatory agencies impose rigorous standards for drug approval, necessitating robust evidence demonstrating that therapeutic agents can effectively reach their target site within the brain. Additionally, the scalability of manufacturing processes for novel drug formulations, particularly those involving complex delivery systems like nanoparticles, can present logistical challenges. Ensuring consistent quality, stability, and reproducibility in drug production is crucial for successful commercialization. In summary, the successful delivery of therapeutics to the brain is hindered by a multitude of factors, including the physicochemical properties of drugs, the dynamic nature of the BBB, the specific characteristics of brain tumors, and the regulatory and manufacturing challenges associated with developing novel drug formulations. To overcome these obstacles, continued research is essential to enhance our understanding of BBB biology and to develop innovative delivery strategies. Advances in nanotechnology, targeted delivery systems, and a deeper understanding of the mechanisms governing drug transport across the BBB and BBTB will play a critical role in improving therapeutic outcomes for CNS diseases and brain tumors. As research progresses, it is hoped that these challenges can be systematically addressed, paving the way for more effective and accessible treatments for neurological disorders.

Current Strategies for Delivering Drugs into the Brain

Significant strides have been made to facilitate the delivery of therapeutic agents and diagnostic tools into the brain. In conjunction with recent progress in understanding the blood-brain barrier (BBB), a variety of novel strategies have emerged. This review encapsulates findings published in the last five years, with some approaches still residing at the proof-of-concept stage. One notable method involves the use of viral vectors, which exhibit a high efficiency in gene transfection. However, challenges such as safety concerns, the need for direct brain injection, difficulties in crossing the BBB, and the requirement for high dosages via intravenous administration are critical limitations to consider (20-23, 25). Nanoparticles represent another promising avenue, enabling actively targeted delivery of drugs while leveraging specific physiological conditions for brain targeting. Nevertheless, a significant challenge remains in their ability to effectively penetrate the BBB (30-31, 33, 36-39, 44, 46, 47, 50). Exosomes are gaining attention for their potential in gene delivery to the brain, primarily due to their possible capability to traverse the BBB. However, challenges include the necessity for exosome donor cells, complexities involved in the loading procedures, and concerns regarding in vivo toxicity and pharmacokinetics (51). Another strategy involves leveraging active transporters in the BBB, which may facilitate the crossing of small molecules into the brain through intravenous injection. Nonetheless, this approach is predominantly limited to smaller compounds (52, 53). Brain permeability enhancers have been identified as a method to transiently open the BBB, but there exists a notable mismatch between findings from rodent studies and human applications (54-58). Furthermore, delivering drugs through the permeable BBB under disease conditions presents the potential for successful drug entry, yet there remains limited understanding of the dynamic changes in the BBB and their underlying mechanisms (63, 70-72, 75-76). Non-invasive techniques aimed at enhancing brain drug uptake offer the potential to open the BBB and reduce the activity of efflux transporters. However, these methods may pose toxicity risks (73, 79-81). Additionally, altering administration routes, such as utilizing nasal administration, can bypass the BBB, although this method is generally suitable only for low doses (83). Finally, nanoparticles designed for brain imaging and diagnostics can enhance imaging capabilities and may cross the BBB, particularly in disease states characterized by increased permeability. Still, understanding the dynamic changes within the BBB remains a significant challenge (10). Overall, these strategies illustrate the ongoing efforts and innovations aimed at improving drug delivery to the brain, each accompanied by specific advantages and limitations that merit further exploration and development.

Viral Vectors

Viral vectors possess a natural capacity to infect cells with nucleic acids, making them a valuable tool for gene delivery, particularly for patients with neurological disorders. Research into the application of viral vectors for this purpose has been ongoing for over two decades. Generally, these vectors exhibit high transfection efficiencies, often around 80% (18). Various types of viral vectors, including lentivirus, herpes simplex virus, adenovirus, and adeno-associated virus (AAV), have successfully achieved gene transduction in the brain. However, the use of viral vectors for drug delivery is accompanied by several limitations, such as difficulties in manufacturing, high production costs, and significant

safety concerns, particularly due to instances of patient fatalities in clinical trials (19, 20). To enable clinical applications, it is crucial to establish the safety of these vectors. Among them, AAV vectors have demonstrated remarkable safety profiles in humans while also being effective for gene delivery within the brain, although concerns regarding their immunogenicity persist (21). Consequently, AAV vectors have emerged as the primary choice for current clinical trials focused on gene therapy for brain disorders. Despite their potential, viral vectors typically cannot passively cross the BBB; however, they can transfect genes into targeted cells. Various administration routes have been explored to either mechanically or biologically bypass the BBB, including stereotaxic injection and administration into the cerebrospinal fluid (CSF) (22). While these methods are specific, they entail significant risks associated with highly invasive neurosurgery. For instance, the AAV2CUhCLN2 vector, utilized for treating late infantile neuronal ceroid lipofuscinosis, required twelve cortical injections via six burr holes, resulting in serious adverse effects reported during clinical trials, although it remains unclear whether these adverse effects were directly related to the AAV2CUhCLN2 vector (23).

Currently, new viral vectors are being developed to address various brain diseases; however, most approaches still rely on direct brain injection (24, 25). Therefore, ensuring safe and systemic delivery remains a critical focus in the development of innovative viral vectors for brain gene therapy. Several AAV serotypes have shown potential to bypass the BBB and effectively target central nervous system (CNS) cells (23, 26, 27). Foust et al. were the first to illustrate extensive transduction of neonatal neurons and adult astrocytes in mice through the intravenous administration of AAV9 at a high dose of 2 x 10^4 vg/kg (28). To identify optimal AAVs capable of crossing the BBB, Zhang et al. evaluated nine recombinant AAVs (rAAVs) for CNS transduction following intravenous injection. The performance of rAAVrh.10 was found to be comparable to that of rAAV9, further confirming the ability of rAAVs to penetrate the CNS in neonatal mice (26). In another study, Vagner et al. intravenously injected AAV9-gfaABC1D-glutamate transporter 1 (GLT1)-Tomato into mice with Huntington's disease, achieving 30% and 49% gene transduction in the striatum and cortex, respectively (23). Despite these advancements, additional studies on novel vectors are necessary to further reduce the required dose, enabling AAV-based therapies to be translated to human applications. Overall, systemic delivery represents a significant unmet need when utilizing viral vectors for CNS gene therapy, and advancements in new vectors and delivery technologies will accelerate the transition from preclinical to clinical studies.

Non-Viral Nanoparticles

Nanoparticles are now a promising strategy for improving medicine delivery across the blood-brain barrier (BBB) thanks to the development of nanotechnology. The literature on this subject has a large number of in-depth reviews (29–31). The purpose of this review is to highlight new research that aims to reinterpret established ideas in this field of study. The ability of nanoparticles to pass the blood-brain barrier is a crucial factor to consider when using them to deliver drugs to the brain. In general, nanoparticles have benefits like regulated drug release, multifunctionality, the capacity to transport therapeutic payloads, and adjustments to the drug's pharmacokinetics. Additionally, nanoparticles can enter "leaky" tumor tissues because of their nanoscale size (usually less than 200 nm), which facilitates drug administration through the increased permeability and retention (EPR) effect (32). Nevertheless, a higher drug concentration in the brain brought about by nanoparticles does not always mean that their tiny size allows them to pass across a healthy blood-brain barrier. Unlike traditional formulations, nanoparticles have the potential to increase medication concentrations at the surface of BBB cells or prolong the drug's duration in circulation in the bloodstream. For instance, nanoparticles of the poly(ethylene glycol)-poly(lactic acid) (PEG-PLA) block-copolymer protein complex cannot penetrate a healthy blood-brain barrier (33); however, they successfully transported brain-derived neurotrophic factor (BDNF) to the brain, increasing the effectiveness of treatment in a mouse model of stroke caused by middle cerebral artery occlusion (34). The PEG-PLA BDNF complex most likely reached the brain through a damaged blood-brain barrier as a result of the stroke (33). Furthermore, the complex most likely lengthened BDNF's plasma half-life, which helped explain the improved therapeutic results shown in mice. As a result, there is still much disagreement about whether nanoparticles or the payloads they contain can pass through the blood-brain barrier (29, 31, 35).

To make it easier to track nanoparticles at the cellular level, Medina et al. recently created "barcoded" poly(lactic-co-glycolic acid) (PLGA) nanoparticles with quantum dots (QDs) (36). Although the QD-PLGA nanoparticles were unable to cross the blood-brain barrier in healthy brains, they were able to enter the central nervous system (CNS) through the leaky vasculature of late-stage intracranial malignancies or circumventricular organs. The capacity of nanoparticles to pass through the leaky BBB is influenced by a number of parameters, including as size, shape, and surface characteristics (30). For example, it has been demonstrated that surfactants like poloxamer 188 and polysorbate 80 improve the ability of nanoparticles to transport medications across the blood-brain barrier after intravenous administration.

Polysorbate 80 or poloxamer 188, when overcoated on nanoparticles, has been shown in numerous studies to adsorb apolipoprotein A-I (Apo A-I) and/or apolipoprotein E (Apo E) from the bloodstream, causing receptor-mediated endocytosis and subsequent transcytosis across the blood-brain barrier (37). Whether a nanoparticle is lipid-based, polymeric, dendritic, or inorganic, its destiny can vary greatly. Furthermore, it can be difficult to isolate specific characteristics and only look at how size affects results in an experimental context. But mounting data points to the oversimplification of the claim that nanoparticles can pass through the blood-brain barrier based just on their small size. The development of novel multispectral techniques, including using QD-labeled PLGA nanoparticles, is expected to provide a more nuanced knowledge of the various fates of nanoparticles within the brain.

The targeted delivery of nanoparticles across the blood-brain barrier (BBB) using transporter or receptor ligands has been under investigation for over three decades. In this method, the ligand acts as a facilitator rather than a drug, aiding in the delivery of therapeutic agents encapsulated within nanoparticles (38). The primary mechanism for this strategy is receptor- or transporter-mediated transcytosis, which allows cargo (e.g., nanoparticles) to move between the apical and basolateral surfaces of brain endothelial cells (ECs). For instance, low-density lipoproteins are transported through ECs via a receptor-mediated process, avoiding the lysosomal pathway and releasing their cargo at the basolateral side of the brain (39). However, the question of whether actively targeted nanoparticles effectively transport drugs to the brain remains debated. RVG29, a 29-amino acid fragment derived from the rabies virus glycoprotein, has been employed to create brain-targeted Pluronic-based nanoparticles, showing improved brain delivery following intravenous administration in mice (40). Additionally, RVG29 has been conjugated with dendrimers and complexed with DNA to produce nanoparticles that preferentially accumulate in the brain after intravenous injection in mice, crossing brain capillary ECs via clathrin- and caveolae-mediated endocytosis (41). Nevertheless, some research indicates that nanoparticles might not be taken up by cells and that the increased drug absorption in the brain may be non-specific (29, 42, 43). For example, Cook et al. found that RVG29-coated PLGA nanoparticles loaded with camptothecin enhanced the drug's delivery to the brain through improved interactions with gamma-aminobutyric acid B receptors on the surface of brain ECs, but did not observe internalization of the nanoparticles in target tissue, concluding that drug transfer occurred non-specifically (35). Similarly, Chen et al. investigated the release of hydrophobic fluorescent probes from fluorescently labeled polymeric micelles using Förster resonance energy transfer imaging. They discovered that the hydrophobic probes were released from the micelles into the extracellular space of tumor cells before the micelles were taken up, suggesting a membrane-mediated pathway for cellular entry (42). Collectively, these findings demonstrate that despite utilizing the same targeting ligand (RVG29), the mechanisms by which drug uptake in the brain is enhanced differ among the nanoparticles employed. These conflicting results highlight the complexities and variations among nanoparticles and underscore critical considerations for the design and evaluation of actively targeted nanoparticles intended to cross the BBB.

Moreover, when employing actively targeted strategies, it is essential to consider the disease condition and progression in nanoparticle design. Ligands are chosen to specifically target an internalizing receptor on the apical side of brain ECs; however, the expression of these receptors and transport mechanisms may alter as the disease progresses. For example, transferrin receptors and insulin receptors are commonly targeted receptors used in developing actively targeted nanoparticles. Research has shown that neuroinflammatory conditions and disease progression can affect the expression of these receptors (44, 45). The iron regulatory protein system (IRPs) governs transferrin receptor expression. A loss of IRPs contributes to neurodegeneration and results in neuronal iron deficiency. Specifically, the genetic loss of IRPs leads to decreased expression of transferrin receptors in IRP2-Null mice (46). Thus, targeting transferrin receptors with nanoparticles may not be an effective means of delivering drugs to the brain under these specific disease conditions. Furthermore, the impact of disease states on receptor expression is highly specific and requires individual assessment. Ho et al. indicated that the total amount of insulin receptors in the brains of non-diabetic sporadic Alzheimer's disease (AD) patients did not significantly change, although they noted impaired insulin receptor signaling (47). Nga Bien-Ly et al. assessed transferrin receptor levels in brain samples from both AD animal models and patients, finding no decreases (48). Therefore, the regulation of transporter or receptor expression at the BBB during disease conditions is not fully elucidated, necessitating detailed studies on this aspect prior to selecting receptors for actively targeted drug delivery.

Recently, novel strategies for nanoparticle-mediated drug delivery to the brain have emerged. One such study utilized propionylated amylose helix to create nanoclusters for encapsulating propofol, a hydrophobic sedative, in rabbits. The higher content of phosphatidylethanolamine (POPE) in brain ECs compared to other ECs facilitated hydrogen bonding between propionylated amylose and POPE, leading to complex binding to the POPE bilayer surface and triggering drug release. This process generated a local high concentration gradient, enabling the hydrophobic

drug to cross the BBB. Molecular dynamics simulations were employed to select the helix and model drug encapsulation and release (49). This innovative approach emphasizes targeting the brain by leveraging specific physiological conditions to initiate drug release rather than merely crossing the BBB. Lipoproteins, which are natural nanoparticles, have been researched as drug delivery vehicles for many years. However, challenges such as scalability and drug loading hinder their application. To address these issues, synthetic mimics of high-density lipoproteins (HDLs) made from natural or synthetic lipids and recombinant apolipoproteins have been developed as alternatives. Song et al. created Apo E-reconstituted HDLs from recombinant Apo E and synthetic lipids to deliver α-Mangostin, a polyphenolic compound, to inhibit Aβ oligomer formation and enhance Aβ cellular degradation. Their findings indicated that Apo E-reconstituted HDLs targeted Aβ aggregates and facilitated BBB penetration (50). To streamline the preparation process and enable scalable production of HDL nanoparticles, our group engineered novel HDL-mimicking nanoparticles using a 3-minute homogenization technique. Natural lipids were employed to construct these nanoparticles through self-assembly, successfully encapsulating nerve growth factor (NGF). The NGF HDL-mimicking nanoparticles preserved the bioactivity of NGF, promoting neurite outgrowth in PC12 cells and extending NGF circulation in mice (51, 52). In contrast to creating mimicking HDL nanoparticles, Rajora et al. developed porphyrin-lipid nanoparticles coated with Apo E3 to target glioblastoma. The Apo E3 porphyrin-lipid nanoparticles specifically targeted low-density lipoprotein receptors, which are overexpressed on glioblastoma cells, facilitating the transcytosis of nanoparticles across the BBB. Their results revealed selective uptake of porphyrin by tumor tissues relative to healthy tissues. Given porphyrin's dual function for fluorescence imaging and photodynamic therapy, the novel Apo E3 porphyrin-lipid nanoparticles hold potential as theranostic agents. However, the authors primarily demonstrated the efficacy of photodynamic therapy in glioblastoma cells, although imaging was assessed in an orthotopic U87-GFP tumor mouse model.

Delivering drugs to brain tumors presents significant challenges, as the drug must not only traverse the blood-brain barrier (BBB) but also infiltrate solid tumor tissues. Angiopep-2 is a peptide ligand specifically designed to interact with low-density lipoprotein receptor-related protein-1 (LRP-1) to facilitate LRP-1-mediated transcytosis. The ability of angiopep-2 to penetrate the brain was illustrated through a conjugate of angiopep-2 and paclitaxel, referred to as ANG1005, which is currently undergoing phase II trials (54). To further enhance penetration in gliomas, a cell-penetrating peptide was attached to the angiopep-2 paclitaxel conjugate. This novel combination of agents—one targeting brain penetration and the other promoting tumor infiltration—significantly enhanced the translocation of paclitaxel into tumor tissues and improved survival rates in a glioblastoma mouse model (55).

Exosomes

Exosomes are small extracellular vesicles secreted by cells, offering a significant advantage over synthetic nanoparticles due to their non-immunogenic nature, which results in prolonged and stable circulation. Components of exosomes isolated from brain endothelial cells (ECs) act as regulators for molecular exchange across the blood-brain barrier (BBB) and facilitate cell-cell communication within the brain (56). Exosomes have been effectively utilized to deliver small molecules, proteins, and nucleic acids across the BBB, as detailed in a comprehensive review (57). Among these applications, the delivery of small interfering RNAs (siRNAs) to the brain is particularly noteworthy. Despite the therapeutic potential of siRNAs, their delivery to the brain presents substantial challenges. Yang et al. successfully isolated exosomes from brain EC culture media and loaded them with vascular endothelial growth factor (VEGF) siRNA using a transfection reagent. This approach enabled the exosomes to facilitate the crossing of siRNA through the BBB, inhibiting VEGF in xenotransplanted zebrafish models bearing brain tumors (58). However, several critical challenges remain for exosomes as drug carriers in clinical settings, including the selection of exosome donor cells, optimization of loading procedures, assessment of siRNA loading efficiency, formulation purification, as well as toxicity and pharmacokinetic studies. Addressing these issues is essential for unlocking the full potential of exosomes in drug delivery.

Delivery of Drugs Through Active Transporters in the Blood-Brain Barrier

Endogenous amino acids access the brain via specific transport systems within the BBB. Leveraging this knowledge presents a promising strategy for drug delivery by conjugating drugs with amino acids that can actively cross the BBB. Peura et al. synthesized three amino acid prodrugs of dopamine to enhance brain uptake through the large amino acid transporter in the BBB. Their in situ rat brain perfusion studies indicated that the phenylalanine prodrug exhibited superior receptor affinity and brain uptake compared to the other prodrugs (59). In a recent study, Singh et al. developed a methotrexate (MTX)-lysine conjugate to facilitate MTX brain uptake utilizing the endogenous lysine transport system. This conjugate demonstrated favorable pharmacokinetics and biodistribution, confirming selective brain transport of the prodrug (60). However, the size limitations of amino acids render this prodrug strategy primarily applicable to small molecules. For macromolecules like proteins and siRNAs, the amino acids may be too small to alter uptake pathways, or the macromolecules

may be too large to utilize these transport systems effectively.

Brain Permeability Enhancers

Several molecules have shown potential in transiently opening the BBB, enabling higher concentrations of systemically administered chemotherapeutics to penetrate the brain (61). The mechanism behind these molecules often involves the temporary disruption of the BBB through decreased expression of tight junction (TJ) proteins such as claudin-1, occludin, and tricellulin. Initial applications included intra-arterial mannitol combined with chemotherapy agents for brain tumor treatment (54). Currently, cereport, a bradykinin analog, has demonstrated an ability to enhance BBB permeability, thereby improving the efficacy of co-administered anti-cancer drugs in animal models. However, clinical trials did not show significant benefits in glioma patients from this co-administration (62). Similarly, regadenoson, an adenosine receptor agonist, increased BBB permeability in animal studies, yet failed to influence the penetration of co-administered contrast agents in humans (61). This discrepancy between rodent and human results highlights the need for further investigation into dosing, scheduling, and combination regimens. Recently, borneol has emerged as a compound to improve both oral absorption and brain penetration of drugs in animal models (63-65). Yi et al. compared four different oral formulations of puerarin with borneol, finding that a self-microemulsifying drug delivery system containing both puerarin and borneol significantly increased area under the curve (AUC) values in both plasma and the brain compared to other formulations (65). It appears that the co-administration of a drug and a permeability enhancer alone may not yield the desired effects in humans, as evidenced by previous studies with cereport and regadenoson. Given that the interaction of enhancers with the BBB is transient, co-delivering both the enhancer and the drug via a single carrier may be crucial for effective drug transport across the BBB during the enhancer's action.

Drug Delivery via the Permeable Blood-Brain Barrier in Disease States

The blood-brain barrier (BBB) has long been recognized as a significant obstacle in the delivery of therapeutics to the brain. While it is established that the permeability of the BBB can increase under certain pathological conditions, comprehensive insights regarding the duration and magnitude of BBB openings remain inadequately defined. Recent investigations have unveiled novel mechanisms underlying these phenomena. For instance, the release of glutamate in endothelial cells has been shown to enhance BBB permeability (66). Furthermore, advancements in brain imaging technologies have yielded more granular data concerning the leakiness of the BBB. This section revisits the longstanding notion of BBB integrity in light of contemporary discoveries related to its permeability during disease states. BBB disruptions have been observed in various conditions characterized by inflammation, trauma, and neurodegeneration. In many instances, the opening of the BBB serves as a key clinical indicator (67). The interendothelial junctions are crucial structures that uphold tissue-fluid equilibrium in a healthy brain. Under specific disease circumstances, protein-rich fluids can infiltrate the interstitium through compromised interendothelial junctions, leading to edema (6, 68). Conversely, brain injuries can further alter BBB permeability as diseases progress (69).

Magnetic resonance imaging (MRI) has emerged as a prevalent non-invasive method for assessing BBB impairment in clinical settings (70-73). Inflammation is recognized as a primary factor contributing to BBB disruption. For example, MRI techniques were employed in patients undergoing cardiopulmonary bypass, which incites a systemic inflammatory response. Abrahamov et al. utilized dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and diffusion-weighted imaging to evaluate BBB disruption and the timeline for recovery of BBB integrity following cardiopulmonary bypass (70). Their findings indicated that BBB integrity was compromised postoperatively, and although permeability recovered within several days, this brief disruption correlated with postoperative neurocognitive deficits. Wong et al. demonstrated that DCE-MRI can be calibrated to provide moderate-to-excellent reproducibility in detecting subtle BBB leaks in individuals with cerebrovascular diseases (72).

Another critical area of inquiry is the dynamic alterations in BBB permeability and their underlying mechanisms following ischemic stroke. The timing of BBB disruption in the context of a stroke remains contentious. Some research suggests that BBB integrity may be compromised hours after the stroke onset (34). However, a recent study employing enhanced MRI techniques indicated a continuous increase in BBB leakage immediately following acute ischemic stroke (AIS), with peak permeability observed between 6 to 48 hours post-onset. The degeneration of the BBB after AIS may precipitate pathological processes such as edema and hemorrhagic transformation (75). Additionally, serial sampling methods for cerebrospinal fluid (CSF) were employed in a non-human primate model of middle cerebral artery occlusion to assess dynamic changes in BBB permeability through the CSF/serum albumin ratio. The results indicated that BBB disruption occurs rapidly after ischemia and is closely correlated with disease progression (76). Focusing on the compromised BBB, Ishili et al. delivered PEGylated liposomes to ischemic regions of the brain during the early phases of reperfusion (77). They further encapsulated Fasudil, a neuroprotective agent, within the liposomes and combined it with tissue plasminogen activator (tPA) for treating ischemic

stroke, finding that pre-administration of liposomal Fasudil prior to tPA resulted in significant neuroprotective effects (78).

To leverage the permeable BBB for drug delivery through nanoparticles, understanding the optimal size of nanoparticles for traversing the leaky BBB is essential. The enhanced permeability and retention (EPR) effect, resulting from the angiogenesis associated with tumors, is particularly relevant in brain tumors, characterized by highly permeable vasculature and a lack of lymphatic drainage (79-81). To effectively exploit the EPR effect for brain tumors, it is vital to comprehend the interplay between the properties of nanoparticles (e.g., particle size) and the physiological dimensions of pores within the blood-brain tumor barrier (BBTB). Dendrimers, as synthetic nanoparticles, allow for controlled design of size, porosity, and surface charge during their synthesis. Exploiting this synthetic versatility, polyamidoamine (PAMAM) dendrimers (generations 1 to 8) were synthesized to examine the impact of nanoparticle size on accumulation within malignant glioma cells in glioma-bearing rats (82). The results revealed that Gd-chelated dendrimers required a maximum size of 12 nm to effectively cross the BBTB, as particles larger than this threshold were unable to penetrate. Furthermore, nanoparticles measuring 4-10 nm in diameter maintained elevated blood concentrations for extended durations in the animal model (83). In a recent investigation, a dual MRI and near-infrared (NIR) imaging agent was developed by conjugating an MRI contrast agent with an NIR fluorescent dye attached to a G5 PAMAM dendrimer (7.6 nm). Both MRI and fluorescence imaging successfully identified the agent within glioma tissue, distinguishing it from normal contralateral tissue (80). Therefore, dendrimers sized below 12 nm may possess the potential to traverse the BBTB. However, synthesizing nanoparticles of varying sizes from identical materials poses challenges, particularly for lipid nanoparticles, complicating the isolation of other influencing factors (e.g., surface characteristics and morphology). Consequently, the relationship between particle size and BBB or BBTB permeability remains ambiguous for alternative nanoparticle types.

Moreover, research has demonstrated that several adjunct therapies for brain diseases may aid in restoring BBB integrity. Bevacizumab, a humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF), is frequently administered to patients with malignant gliomas at advanced stages. By influencing the vasculature of brain tumors, this treatment has been shown to restore BBB function (84). However, the long-term implications of combining Bevacizumab with other drugs in the therapeutic regimen on brain drug uptake remain a pertinent consideration. A comprehensive understanding of the dynamics of the BBB may provide valuable insights for future therapeutic strategies in treating brain disorders. It is plausible that the BBB may not pose a significant barrier if interventions are timed appropriately during critical periods of BBB permeability. Thus, addressing the current challenges in brain drug delivery could potentially be achieved by strategically exploiting certain pathological states.

Non-invasive Techniques to Enhance Drug Uptake in the Brain

Recent advancements have positioned ultrasound as a promising method for facilitating the transgression of drugs across the blood-brain barrier (BBB). Microbubble-enhanced diagnostic ultrasound (MEUS), a non-invasive approach, has effectively increased the permeability of the blood-brain tumor barrier (BBTB) in glioma cases. Key proteins in tight junctions (TJs) of the BBB, including claudins, occludin, and junctional adhesion molecules (JAMs), can be downregulated through ultrasound irradiation and microbubble application, resulting in a temporary opening of the BBB without inflicting damage to surrounding healthy brain tissue (79, 85). Furthermore, Ningaraj et al. demonstrated that MEUS elevates the expression of calcium-activated potassium (KCa) channels in gliomas, which promotes pinocytosis and enhances BBTB permeability (79). Despite improvements in BBTB permeability, the BBB continues to pose a challenge for drug delivery in brain tumors. The integration of focused ultrasound (FUS) with microbubbles has shown to enhance the permeability of both the BBTB in brain tumors and the BBB in adjacent tissues. Park et al. utilized dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) to investigate doxorubicin delivery through this combined approach in both rat brain tumors and normal brain tissues. Their findings indicated that this method significantly extended drug retention time within the tissue for over 24 hours while facilitating the passage of doxorubicin across both the BBB and BBTB (86). Notably, MEUS was observed to temporarily inhibit P-glycoprotein (P-gp) expression; suppression lasted up to 48 hours and returned to baseline levels by 72 hours, with the degree of suppression modifiable via instrumentation adjustments (87). To elucidate the physiological alterations within the brain following FUS-induced BBB opening, non-human primates were subjected to varying acoustic pressures. Pharmacokinetic analyses confirmed that FUS effectively and temporarily opened the BBB, enhancing drug delivery. The degree of BBB permeability was influenced by brain inhomogeneity and acoustic pressure, which ultimately affected drug concentration within the brain (88). Comprehensive discussions on the fundamental principles and prospects of ultrasound-mediated drug delivery are documented elsewhere (89).

In addition to FUS, transcranial magnetic stimulation (TMS) has emerged as another method to promote drug delivery by stimulating neuronal activity and enhancing glutamate release across the BBB. A preliminary clinical trial reported that TMS improved

BBB permeability in 10 out of 15 patients with malignant brain tumors, highlighting its potential applicability in clinical settings to enhance drug delivery to the brain (66).

Alteration of Administration Routes

The intranasal route presents a promising method for delivering drugs directly to the brain, circumventing the BBB via the olfactory pathway. Many therapeutics aimed at treating human immunodeficiency virus (HIV) exhibit low bioavailability due to the first-pass effect and limited BBB permeability. The central nervous system (CNS) is recognized as a crucial reservoir for HIV. To enhance bioavailability and brain uptake, efavirenz was encapsulated in solid lipid nanoparticles using high-pressure homogenization. This formulation led to a more than 150-fold increase in efavirenz concentration within the brain via intranasal administration compared to oral delivery (90). However, the primary limitation of intranasal administration lies in the maximum drug volume that can be effectively delivered through the nasal cavity, making this route particularly suitable for highly potent drugs.

Nanoparticles for Brain Imaging and Diagnostics

Nanoparticles have been extensively investigated for tumor imaging and diagnostics; however, research focusing on CNS diseases remains limited, likely due to the challenges presented by the BBB. Advances in imaging modalities, especially MRI and computed tomography (CT), have significantly improved the management and prognosis of neurodegenerative conditions. BBB disruption can be quantitatively evaluated using DCE-MRI in patients suffering from ischemic stroke (73). Additionally, multimodal MRI techniques have been employed to monitor the dynamic progression of injury and BBB disruption following intracerebral hemorrhage, a major contributor to morbidity and mortality (91). Beyond diagnostics and therapeutic monitoring, quantitative assessments of BBB permeability may facilitate the selection of appropriate interventions beyond established time frames. Tissue plasminogen activator (tPA) is the primary treatment for acute stroke; however, its use can precipitate hemorrhage. Research utilizing CT angiography indicated that hemorrhagic transformation correlates with increased BBB permeability, thereby suggesting CT as a valuable tool for assessing hemorrhage risk prior to tPA administration (92). Furthermore, gadolinium micelles, developed as MRI contrast agents for tumor imaging (93), were utilized to evaluate BBB permeability in a rat model. Significant contrast regions were detected in the ischemic hemisphere, indicating BBB permeability for macromolecules. Due to their elevated molecular weight, these gadolinium micelles remained localized within the ischemic region, allowing visualization of BBB openings for hemorrhage risk assessment.

Nasal to Brain Delivery:

The intranasal (IN) route serves as a non-invasive or minimally invasive method for delivering drugs to the central nervous system (CNS), proving to be more effective than both intravenous (IV) and oral administration routes. By providing a direct pathway to the CNS, the IN route can circumvent the blood-brain barrier (BBB) while also minimizing systemic side effects. In contrast, parenteral routes and oral administration necessitate that drugs first navigate several barriers to achieve systemic circulation before they can cross the BBB to access the CNS. Furthermore, the IN route avoids hepatic first-pass metabolism and the degradation of drugs within the gastrointestinal tract, making it a viable alternative for parenteral administration, particularly for biopharmaceuticals such as proteins and peptides. Therefore, IN administration allows for direct drug delivery to the brain, primarily via the sensory neuronal pathway or indirectly by traversing the BBB from systemic circulation. The nasal cavity consists of three main regions: the vestibular region, the respiratory region, and the olfactory region . The vestibular region, the outermost section of the nasal cavity, is lined with ciliated hairs and a mucous layer that obstructs the entry of external particles, antigens, and pathogens. The respiratory region contains trigeminal sensory nerves and blood vessels, while the olfactory region, situated in the upper portion of the nasal cavity, is composed of an epithelium made up of supporting cells, basal cells, and olfactory sensory neurons. This area is closely connected to the brain's olfactory bulb (OB) through olfactory nerves that lie just beneath the cribriform plate of the skull, with trigeminal nerves also present in this region [94-95]. Upon depositing a therapeutic formulation within the nasal cavity, it must navigate past mucociliary clearance mechanisms in the vestibular region. Once it reaches the inner nasal cavity, the drug can access the CNS via the olfactory or trigeminal nerves or indirectly through the systemic circulation. The trigeminal and olfactory pathways enable direct delivery to the brain, positively influencing the pharmacokinetic and pharmacodynamic (PK/PD) profiles of CNS drugs. With respect to the olfactory pathway, the drug can reach the OB after traversing the olfactory mucosa or the cerebrospinal fluid (CSF), where it subsequently mixes with interstitial fluid in the brain. For therapeutic agents to effectively reach the brain, they must pass through the cribriform plate and the olfactory nerve after engaging with olfactory receptors on olfactory neurons. The mechanisms for direct drug delivery to the brain via olfactory nerves include both intraneuronal and extraneuronal transport

pathways, where the former occurs along axons and the latter through perineural channels [95].

The trigeminal pathway consists of branches from the trigeminal nerves supplying both the respiratory and olfactory mucosa, which transport therapeutically active compounds toward the brain stem and associated tissues. These branches penetrate the brainstem at the level of the pons and extend to both the hindbrain and forebrain. This pathway facilitates intracellular transport along axons and extracellular transport via diffusion and bulk flow through perineuronal channels, perivascular spaces, or lymphatic channels linked to the CSF and brain tissues. The physicochemical characteristics of the drug play a critical role in determining whether transport will occur intracellularly or extracellularly [96]. Conversely, the respiratory region is highly vascularized, which promotes systemic drug absorption. Small lipophilic molecules have a greater propensity to cross the BBB more readily than hydrophilic and high molecular weight compounds. Once the drug enters the nasal blood vessels, it can reach the carotid artery and subsequently the brain and spinal cord. However, this route is less preferred due to the limitations imposed by the BBB on drug access to the CNS and the potential for undesired peripheral effects resulting from systemic distribution [97]. Despite the advantages and potential of the nose-to-brain administration route, significant challenges remain for drugs attempting to reach the CNS, which include the anatomical, physiological, and biochemical characteristics of the target site.

One major challenge arises from the presence of mucus in the nasal mucosa, combined with ciliary movement, as these factors constitute the primary barriers to overcome when drugs are administered via the IN route. Both mucus and ciliary activity can limit the retention time of the drug formulation in the nasal cavity and hinder molecular movement toward the CNS. Additionally, the small volume available for formulation delivery in each nostril may impede effective brain drug delivery [98]. The anatomical positioning of the olfactory epithelium also presents a significant limitation, as the dosage form must first reach this site. Furthermore, metabolic enzymes present in the olfactory mucosa must be considered when designing a formulation intended for the nose-to-brain route. Consequently, IN formulations should consist of biocompatible and odorless excipients, avoiding rapid elimination due to mucociliary clearance and/or enzymatic degradation. Moreover, these formulations must exhibit suitable viscosity, physiological tonicity, and a pH compatible with the nasal mucosa. Various strategies have been explored to address the challenges associated with this route of administration. Many of these approaches aim to enhance molecular absorption and permeability by prolonging the time the dosage form remains in the nasal mucosa while increasing drug concentration within the CNS [99]. Strategies include the use of permeation and absorption enhancers, cell-penetrating molecules, mucoadhesive and mucopenetrating agents, enzyme inhibitors, hydrogel systems, and nanoparticulate drug delivery systems, or combinations thereof. In particular, nanoparticulate-based systems have shown remarkable potential in overcoming the challenges associated with the IN route, effectively promoting drug accumulation in the brain while minimizing systemic distribution.

Nanoparticles for Nose-to-Brain Drug Delivery

Nanoparticle-based systems have significantly advanced strategies for delivering therapeutic agents to the central nervous system (CNS) due to their functional properties associated with the nanometer scale and material composition. These nanoparticles can effectively cross the blood-brain barrier (BBB) owing to attributes such as surface area, reactivity, strength, sensitivity, and solubility. Various methods can facilitate the delivery of nanoparticle-based systems to the CNS, including non-invasive, invasive, and alternative routes [100]. Non-invasive methods leverage endogenous cellular mechanisms that facilitate the transport of nanoparticles across the BBB through transcellular pathways, influenced by their colloidal, chemical, or biological properties. Invasive techniques, on the other hand, involve directly administering nanoparticulate systems into brain tissue via intraventricular, intrathecal, or interstitial injections, as well as utilizing methods that disrupt the BBB through osmotic, ultrasound, chemical, or magnetic strategies. Despite the challenges faced, intranasal (IN) administration of nanoparticulate systems remains the most promising approach for delivering therapeutic agents to the CNS. The advantages associated with this administration route, combined with the unique properties of nanoparticles, can facilitate targeted drug delivery to the CNS. The size of nanoparticulate systems is a crucial factor that must be controlled in the design of IN formulations. Particle size significantly impacts drug loading, release, and stability, ultimately determining in vivo distribution, toxicity, and targeting efficacy toward the CNS. Moreover, particle size distribution influences the pharmacokinetics of nanocarriers, affecting circulation time, absorption, and biodistribution [101]. Smaller particle sizes and larger surface areas can enhance drug solubility, interaction with the mucosa, and permeation compared to traditional drug solutions. This can be further optimized by the composition of the nanoparticulate system.

The surface charge of nanocarriers also plays a vital role in enhancing drug performance post-administration. Positive zeta potentials facilitate better interactions with negatively charged mucin residues, promoting prolonged retention of the formulation in the nasal mucosa. IN nanoparticle-based systems have demonstrated improved permeability and absorption of drugs, as well as enhanced uptake in the olfactory region, leading to increased access and accumulation in the CNS. Additionally, they can protect therapeutic

agents from degradation and prevent their transport by efflux transporters [102]. The integration of nanotechnology with other strategies has further augmented the accumulation of IN nanoparticulate systems in the CNS. Surfactants, such as pegylated molecules, are employed to enhance drug permeation [103], while mucoadhesive polymers like chitosan, which interact with mucin, help extend the residence time of formulations in the nasal cavity [104]. Furthermore, incorporating cell-penetrating peptides (CPPs) that can engage biological membranes promotes cellular uptake [105-106]. Additionally, numerous studies have explored the use of biorecognition ligands to enhance nose-to-brain transport of nanocarriers. For instance, proteins with receptors in the olfactory region, such as lectins, are considered the gold standard for active brain targeting [107-108].

Influence of Aging on the Blood-Brain Barrier

A neglected issue in the literature and research is the influence of aging on brain drug delivery. This section summarizes key findings from the literature. The blood-brain barrier (BBB) is composed of brain microvascular endothelial cells (ECs), astrocytes, pericytes, neurons, and the basement membrane. Aging can impact these components of the BBB. For example, studies have shown that genes related to inflammation and scar formation are upregulated in aged astrocytes [109]. Additionally, astrocytic functions critical for stroke recovery are influenced by aging, as observed in both male and female rats [110-111]. Moreover, with age, astrocytes exhibit a decrease in the secretion of trophic factors that protect against neural degeneration [96-98]. In one study, Okoreeh et al. injected AAV5-GFP-hIGF-1 into the striatum and cortex to transfer the IGF-1 gene to astrocytes in middle-aged female rats. The results indicated that IGF-1 genes facilitated the recovery from stroke-induced damage, including improvements in BBB permeability and neuroinflammation [112]. However, this study did not compare the effects of IGF-1 gene therapy in rats of different ages.

Furthermore, aging affects astrocytes' ability to uptake nutrients in the brain (e.g., glucose) and the expression of corresponding receptors at the BBB (e.g., GLUT-1) [113]. Consequently, nanoparticles designed to target GLUT-1 may not be effective when administered to elderly individuals. In addition to astrocytes, studies have shown a decrease in pericyte numbers with age, which correlates with increased BBB permeability [114]. As aging influences the structure of the BBB, the permeability of molecules is also altered. One study assessed the permeability to nerve growth factor (NGF) in newborn rats with hypoxic-ischemic brain damage, as well as in neonatal and adult healthy rats. The findings revealed that NGF penetration across the BBB was significantly higher in newborn rats under hypoxic conditions compared to both neonatal and adult rats. Moreover, NGF exhibited significantly greater permeation in neonatal rats than in adult rats, highlighting the influence of age on BBB permeability [115]. Additionally, common stresses associated with diseases further compromise BBB function in older patients, despite BBB dysfunction often occurring early in disease pathogenesis. Wang et al. demonstrated that lipopolysaccharide induced BBB disruption in aged mice, mimicking the stress associated with sepsis. Their study found that BBB disruption was linked to the degradation of occludin and claudin-5, suppression of protein kinase activation, and upregulation of gp91phox [116]. Given the limited research and complexity of the topic, the exact influence of aging on the BBB remains unclear, as does the degree of this impact. However, understanding gene expression and permeability of the BBB across different age groups is critical, especially considering the high incidence of many CNS disorders in seniors. Consequently, drug delivery researchers must account for the effects of aging when designing novel drug delivery systems for CNS diseases [117].

Conclusion:

In summary, effective brain drug delivery remains a critical challenge in the treatment of central nervous system (CNS) disorders due to the unique anatomical and physiological barriers presented by the blood-brain barrier (BBB). Traditional routes of administration often fall short in achieving therapeutic concentrations within the brain, necessitating innovative approaches. Recent advancements in drug delivery systems, particularly nanoparticle-based formulations and nasal-to-brain delivery techniques, show promise in enhancing drug permeability and targeting efficacy. Nanoparticles, owing to their nanoscale dimensions and tailored surface properties, facilitate the transport of therapeutic agents across the BBB through various mechanisms. These systems can be engineered to improve solubility, stability, and biocompatibility while minimizing systemic side effects. Moreover, the utilization of mucoadhesive polymers in nasal formulations can prolong the residence time in the nasal cavity, thereby enhancing the absorption of drugs into the CNS via olfactory and trigeminal pathways. However, despite the progress made, several challenges remain. The variability in individual responses due to factors such as age, sex, and genetic background can significantly affect drug pharmacokinetics and pharmacodynamics. Additionally, the development of effective drug delivery systems must account for the potential for neuroinflammation and other adverse effects associated with aging and neurological diseases. Future research should focus on the comprehensive understanding of BBB dynamics and the development of personalized medicine approaches that consider patient-specific factors. The integration of biorecognition ligands and targeted delivery systems could further optimize drug delivery to specific brain regions affected by disease. In conclusion, while

significant strides have been made in brain drug delivery technologies, ongoing research and innovation are essential to overcome existing barriers and improve therapeutic outcomes for patients with CNS disorders. Continued collaboration between neuroscientists, pharmacologists, and biomedical engineers will be crucial in translating these technologies from the laboratory to clinical practice, ultimately enhancing the quality of life for individuals suffering from neurological conditions.

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