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Review Article

Physiological and Pharmaceutical Determinants of Brain Drug Bioavailability: Barriers, Transport Mechanisms, and Advanced Nanotechnological Strategies

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Abstract

Efficient delivery of therapeutic agents to the central nervous system (CNS) remains challenging due to the restrictive blood–brain barrier (BBB). This review evaluates physiological and pharmaceutical determinants of brain bioavailability and discusses emerging nanotechnology-based strategies. Brain bioavailability is influenced by BBB integrity, efflux transporter activity, cerebral blood flow, pathological conditions, molecular properties, and nanocarrier design. Integrating physiological understanding with rational pharmaceutical design is essential for improving future CNS therapeutics.

Keywords: Blood–brain barrier; Brain bioavailability; CNS drug delivery; Efflux transporters; Nanoparticles; Receptor-mediated transport; Intranasal delivery

Introduction

The treatment of central nervous system (CNS) disorders, including neurodegenerative diseases, brain tumors, epilepsy, and psychiatric conditions, remains a significant challenge due to the restrictive nature of the blood–brain barrier (BBB) [1, 2] . The BBB is a highly selective physical and metabolic barrier formed by brain microvascular endothelial cells, pericytes, astrocytic end-feet, and a basement membrane, collectively referred to as the neurovascular unit (NVU) [2, 3]. While this barrier protects neural tissue from toxins and pathogens, it also severely limits the penetration of most therapeutic agents, including small molecules, peptides, and biologics (4, 5). Studies suggest that more than 98% of small-molecule drugs and almost all macromolecules fail to cross the BBB effectively under normal physiological conditions [1, 6] .

The complexity of BBB transport arises from multiple mechanisms that regulate molecular entry into the CNS. These include tight junction-mediated paracellular restriction, active efflux transporters such as P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance proteins (MRPs), enzyme-mediated metabolism, and selective carrier- or receptor-mediated transcytosis [3, 7, 8]. The expression and activity of these transporters are not static; they can be altered by disease states, inflammation, and pharmacological interventions, further complicating the predictability of CNS drug delivery [9-11].

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Pharmacokinetic and physicochemical properties of therapeutic molecules, such as molecular weight, lipophilicity, polarity, ionization, and plasma protein binding, play an important role in determining BBB permeability [12, 13]. For instance, molecules with low molecular weight (<500 Da) and moderate lipophilicity (logP 1–3) tend to cross the BBB more effectively via passive diffusion [12, 14]. However, these characteristics alone are insufficient for achieving therapeutic concentrations in the brain, particularly for complex diseases that require high regional specificity.

Given the limitations imposed by the BBB, alternative drug delivery strategies have gained attention. Intranasal delivery represents a noninvasive approach that exploits the olfactory and trigeminal nerve pathways to bypass the BBB and deliver drugs directly to the CNS [15, 16]. Additionally, nanotechnology-based carriers, including liposomes, polymeric nanoparticles, solid lipid nanoparticles, and exosomes, provide opportunities for improved CNS targeting by enhancing drug stability, prolonging circulation time, and facilitating receptor-mediated transport [17–20]. Recent studies have demonstrated that surface modifications, such as PEGylation or ligand attachment, can significantly improve brain accumulation of therapeutics in preclinical models [18, 19].

Despite these advances, the translation of preclinical findings into clinical success remains limited, highlighting the need for a deeper understanding of the interplay between physiological factors, disease-related BBB alterations, and pharmaceutical design [21, 22]. Furthermore, integration of advanced imaging, computational modeling, and pharmacokinetic analyses is critical to optimize CNS drug delivery and predict therapeutic efficacy [23, 24].

In summary, enhancing brain drug bioavailability requires a multidimensional approach that accounts for the structural and functional complexity of the BBB, the physicochemical properties of therapeutic agents, the pathological state of the CNS, and innovative pharmaceutical strategies. This review aims to provide a comprehensive evaluation of the physiological and pharmaceutical determinants of brain bioavailability, with a particular focus on emerging nanotechnology-based approaches for overcoming BBB limitations.

Physiological Determinants of Brain Bioavailability

Structural and Functional Characteristics of the Blood–Brain Barrier

The BBB consists of endothelial cells, tight junctions, pericytes, and astrocytic end-feet, forming the neurovascular unit [2]. Key characteristics include tight junctions, absence of fenestrations, low pinocytosis, and high electrical resistance. Passive diffusion generally favors small (<500 Da), moderately lipophilic, nonionized molecules [1].

Efflux Transporters and Active Barrier Mechanisms

ATP-binding cassette (ABC) transporters significantly reduce CNS drug accumulation by actively exporting substrates back into systemic circulation. Major efflux transporters include:

- P-glycoprotein (P-gp)
- Breast cancer resistance protein (BCRP)
- Multidrug resistance-associated proteins (MRPs)

Overexpression or high activity of these transporters can dramatically decrease intracerebral drug concentrations, even when passive permeability across the BBB is adequate [3, 4].

Cerebral Blood Flow and Physiological Influences

Cerebral blood flow (CBF), averaging approximately 50 mL/100 g/min in healthy adults, determines the rate at which a drug is delivered to the brain vasculature. Pathological conditions such as ischemia, inflammation, trauma, and tumors can significantly alter CBF, thereby influencing drug distribution kinetics. In certain pathological states, including glioblastoma and neuroinflammatory diseases, BBB integrity may be compromised. Although increased permeability may enhance drug entry locally, the disruption is often heterogeneous, resulting in uneven drug distribution and suboptimal therapeutic outcomes [4].

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Intranasal Drug Delivery

Intranasal administration offers a noninvasive route to bypass the BBB via:

- The olfactory nerve pathway
- The trigeminal nerve pathway

Advantages include rapid onset of action and reduced systemic exposure. However, limitations such as low dosing volume, mucociliary clearance, and enzymatic degradation remain significant challenges [5], with challenges including enzymatic degradation and mucociliary clearance (Table 1) [6].

Table 1. Major factors affecting CNS drug delivery across the BBB

Factor	Description	Mechanism	Clinical impact	Reference
BBB integrity	Tight junctions and neurovascular-unit components, including endothelial cells, astrocytes, and pericytes	Restricts paracellular transport and limits nonspecific transcellular entry	Limits passive drug entry into the brain	[25]
Efflux transporters	ATP-binding cassette transporters, including P-gp, BCRP, and MRPs	Actively export drugs from brain endothelial cells into the circulation	Decreases brain drug exposure and may contribute to treatment resistance	[26]
Cerebral blood flow	Regional cerebral perfusion and capillary drug supply	Determines the rate at which a drug reaches the BBB	Produces heterogeneous CNS exposure; reduced delivery may occur in hypoperfused regions	[27]
Enzymatic metabolism	Drug-metabolizing enzymes in brain microvessels, including CYPs and esterases	Metabolizes or inactivates drugs during passage across the BBB	Reduces the concentration of active drug reaching CNS targets	[28]
Disease state	Stroke, brain tumors, and neuroinflammation	Alters BBB permeability, cerebral perfusion, and transporter activity/expression	Causes dynamic and variable drug penetration; may increase delivery locally but not uniformly	[29]

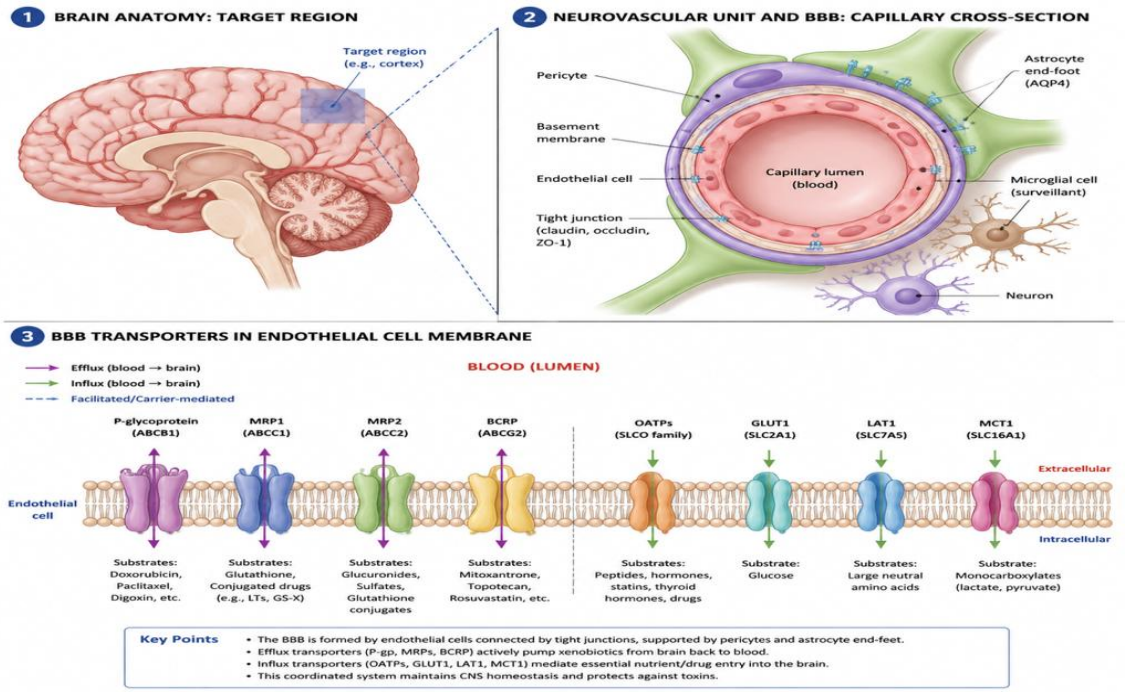


Figure 1. Overview of the blood-brain barrier (BBB) architecture and relevant transport mechanisms. The diagram illustrates the cellular components of the neurovascular unit and the localization of key transmembrane transporters (e.g., P-gp, BCRP, OATPs) that regulate drug delivery to the CNS. (Created using OpenAI DALL·E 3, https://chatgpt.com, and curated by the author).

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Pharmaceutical Determinants of Brain Bioavailability

Physicochemical Determinants

Molecular Weight

Optimal BBB penetration is generally associated with molecular weights below 400–500 Da. Larger molecules typically require carrier-mediated or nanotechnological strategies.

Lipophilicity (Log P)

An optimal LogP range of 1–3 is considered favorable for BBB permeation. Excessive lipophilicity may cause membrane sequestration, whereas insufficient lipophilicity limits passive diffusion.

Degree of Ionization (pKa)

Non-ionized drug fractions exhibit superior transcellular permeability across the BBB, making pKa a critical parameter in CNS drug design.

Plasma Protein Binding

Only the unbound fraction of a drug is available for BBB penetration. High plasma protein binding reduces effective CNS delivery [1, 6].

Nanotechnology-Based Strategies

Nanocarriers have emerged as promising platforms for enhancing brain bioavailability.

Particle Size

Particles below 200 nm are generally preferred, while sizes under 100 nm may facilitate improved endothelial interaction and transcytosis.

Surface Charge

Mildly positive surface charge may enhance interaction with negatively charged endothelial membranes; however, excessive cationic charge can induce cytotoxicity and rapid systemic clearance.

Types of Nanocarriers

- Liposomes
- Solid Lipid Nanoparticles (SLNs)
- Nanostructured Lipid Carriers (NLCs)
- Biodegradable polymeric nanoparticles

These systems can protect drugs from degradation, prolong circulation time, and facilitate receptor-mediated transport [8–10].

Targeted Brain Delivery Systems

Advanced strategies to enhance brain bioavailability include:

Receptor-mediated transcytosis (e.g., transferrin receptor targeting)

Adsorptive-mediated transport

Prodrug design

Efflux transporter inhibition

Such approaches aim to either exploit endogenous transport pathways or circumvent efflux-mediated drug extrusion (Table 2) [11, 12].

Table 2. Pharmaceutical Determinants of Brain Bioavailability

Property	Optimal Range/Consideration	Impact on CNS Delivery	References
Molecular Weight	<500 Da	Better passive diffusion	[1, 7, 30]
Lipophilicity (log P)	1–3	Enhances BBB permeability	[7]
Polar Surface Area	<90 Å²	Favors transcellular diffusion	[7, 30]
Ionization	Mostly non-ionized	Enhances lipid membrane crossing	[7]
Plasma Protein Binding	Low/moderate	Higher unbound fraction	[4]

Preclinical Evidence for Brain-Targeted Delivery

Preclinical evidence strongly supports the feasibility of several brain-targeted delivery strategies, although most findings remain limited to *in vitro* systems and animal models. The blood–brain barrier (BBB) is composed of tightly joined endothelial cells supported by pericytes and astrocytes, and it regulates the entry of most small molecules and essentially all macromolecules into the central nervous system. As a result, more than 98% of low-molecular-weight drugs and nearly all biologics fail to reach therapeutically relevant concentrations in the brain after conventional systemic administration [31].

Among the preclinical strategies investigated, nanoparticle-based systems have received

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considerable attention because they can improve drug stability, prolong circulation time, and enhance BBB crossing through receptor-mediated transcytosis, adsorptive-mediated transcytosis, membrane coating, or stimuli-triggered transport. Surface modification with targeting ligands may further improve interaction with BBB-associated receptors, while tuning nanoparticle size, charge, and composition can influence biodistribution and uptake [31, 33]. Biomaterial-based platforms such as liposomes, polymeric nanoparticles, inorganic nanoparticles, exosomes, and cell-membrane-coated systems have all shown promise in preclinical brain delivery studies [31].

Intranasal administration is another major preclinical approach for bypassing the BBB. This route exploits the olfactory and trigeminal pathways to facilitate direct nose-to-brain transport and can reduce systemic exposure and hepatic first-pass metabolism [32]. Lipid-based nanoparticles, including solid lipid nanoparticles and nanostructured lipid carriers, have shown particular promise in this setting because they can improve solubility, protect cargo from degradation, and support sustained release. However, the short nasal residence time and rapid mucociliary clearance remain important barriers, and *in situ* gel systems have therefore been developed to improve retention and enhance delivery efficiency [32].

Importantly, increased brain accumulation in preclinical models does not necessarily translate into clinical efficacy. Differences in animal species, disease models, BBB integrity, drug dose, analytical methods, and outcome measures make direct comparison across studies difficult [31, 32]. Therefore, while the available preclinical literature supports proof-of-concept for a range of brain-targeted delivery platforms, standardized translational studies are still required to determine their true therapeutic value (Table 3).

Table 3. Comparison of Nanocarriers, including FDA Approval Status, Clinical trial Stage, and Limitations

Nanocarrier	Size	Surface Modification	Targeting Strategy	FDA Approval Status	Clinical Trial Stage	Limitations	References
Liposomes	50–150 nm	PEGylation	Ligand-targeted	**Approved** Multiple formulations approved (e.g., Doxil, Onivyde). Some approvals withdrawn post-market (e.g., Marqibo).	**Phase I to Approved** Extensive clinical history; active Phase III/IV monitoring.	Rapid clearance by RES (if non-PEGylated), PEG-immunogenicity (ABC phenomenon), drug leakage, scale-up reproducibility.	[34–37]
Polymeric NPs (PLGA)	80–200 nm	PEG, functional ligands	RMT, TME targeting	**Excipient Approved** PLGA polymer is FDA-approved for depot systems, but no targeted PLGA NPs are approved yet.	**Phase I/II** Mostly preclinical; limited formulations in early-stage active trials.	Low encapsulation efficiency for hydrophilic drugs, burst release, acidic degradation microenvironment, sterilization issues.	[38–40]

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Solid Lipid NPs (SLNs)	100–200 nm	Surfactants, PEG	BBB modulation	**Not Approved** No SLN-specific formulations have received FDA approval to date.	**Phase I/II** Primarily preclinical; restricted to localized/niche clinical trials.	Low drug loading capacity, drug expulsion during storage due to polymorphic transition, stability limitations.	[41–43]
Exosomes	30–150 nm	Surface engineering	Homotypic targeting	**Not Approved** No FDA-approved exosome products. Regulated strictly as biological drugs.	**Phase I/II** Investigational only; multiple early trials for inflammatory diseases and oncology.	High heterogeneity, low isolation yield, lack of standardization in purification/characterization, cargo loading complexity.	[44–46]

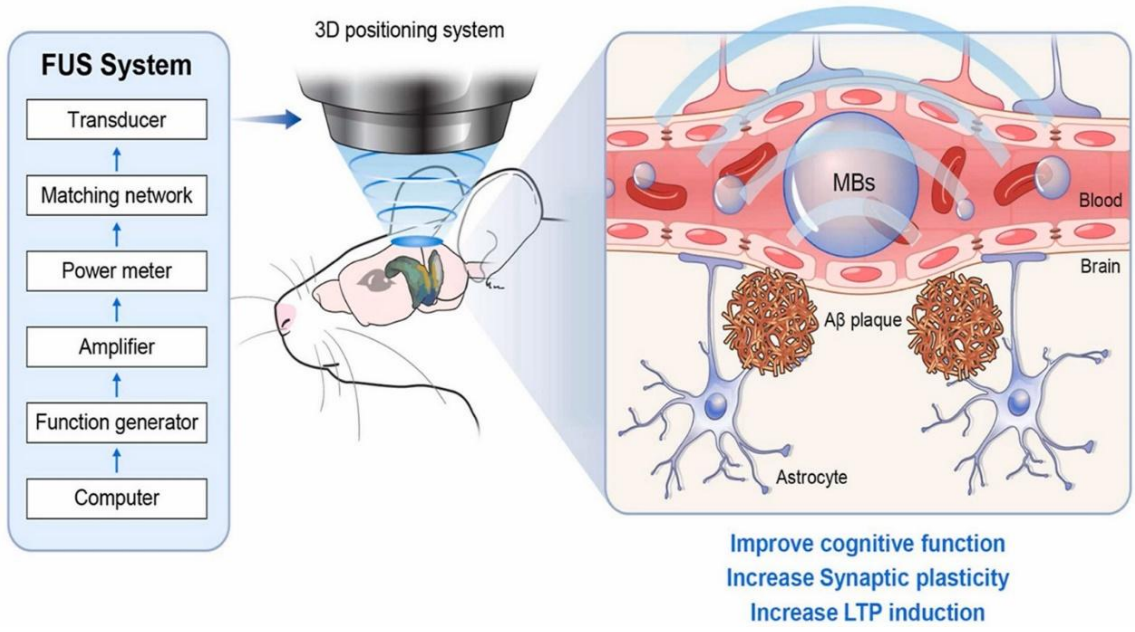


Figure 2. Focused ultrasound with microbubbles transiently opens the BBB for localized drug delivery

Clinical Translation and Current Clinical Use

Despite substantial progress in formulation science, the clinical translation of brain-targeted drug delivery remains limited. The BBB continues to be one of the major obstacles to effective CNS pharmacotherapy, because it restricts the penetration of both small-molecule and biologic therapeutics into the brain parenchyma [31]. Although many delivery platforms have shown promising effects in preclinical models, only a small fraction have advanced to clinical evaluation, and even fewer have demonstrated clear benefit in routine clinical practice.

Intranasal delivery is among the most attractive clinically relevant strategies because it offers a noninvasive route that may bypass the BBB through direct nose-to-brain transport. This approach is particularly appealing for CNS diseases requiring rapid onset or repeated administration. However, successful clinical use depends on factors such as nasal anatomy, mucociliary clearance, formulation residence time, dosing device performance, and interindividual variability [32]. These issues help

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explain why encouraging animal data often overestimate human performance.

Nanocarrier-based strategies also face major translational hurdles. Although nanoparticles can improve circulation time, drug loading, and BBB interaction, their *in vivo* performance is strongly influenced by protein corona formation, off-target uptake, immunological interactions, and accumulation in organs such as the liver and spleen [31, 33]. In addition, large-scale manufacturing, batch-to-batch reproducibility, sterilization, long-term stability, and quality control requirements remain significant barriers to clinical adoption [33].

Therefore, current evidence supports the concept that brain-targeted delivery systems can improve CNS exposure under experimental conditions, but direct clinical evidence remains limited. Future clinical translation will require pharmacokinetic validation, biomarker-guided patient selection, robust safety assessment, and well-designed clinical trials that evaluate meaningful neurological outcomes rather than brain accumulation alone.

Integrated Perspective and Future Directions

Brain bioavailability is determined by physiological barriers, transporters, molecular properties, disease state, and formulation design. Computational modeling and targeted systems represent promising strategies for improving CNS drug delivery.

Discussion

Brain bioavailability is a multifactorial phenomenon governed by intricate interactions between physiological barriers and pharmaceutical design variables. Successful CNS drug development requires a mechanistic understanding of BBB biology, transporter dynamics, and molecular pharmacokinetics. Nanotechnology-based and receptor-targeted strategies represent promising approaches; however, translation from bench to bedside remains constrained by safety concerns and regulatory challenges.

Limitations and Challenges in Brain Drug Delivery

Although brain-targeted delivery technologies have advanced considerably, several limitations continue to restrict their effectiveness and translation. First, the BBB is a highly dynamic and heterogeneous barrier whose permeability varies with disease state, inflammation, transporter expression, and regional vascular differences [31]. In pathological conditions, BBB disruption is often incomplete and uneven, which can result in nonuniform drug distribution and suboptimal therapeutic response.

Second, many nanoparticle systems are affected by off-target distribution and biological instability. Even when nanoparticles are designed for BBB transport, a substantial portion of the administered dose may be cleared by the mononuclear phagocyte system or sequestered in peripheral organs such as the liver and spleen [31, 33]. Surface properties, including size, charge, and ligand density, must therefore be precisely optimized, because excessive cationic charge may increase cytotoxicity and rapid systemic clearance [31].

Third, intranasal delivery has practical and biological limitations. Although the route is noninvasive and clinically appealing, it is constrained by limited nasal dosing volume, mucociliary clearance, enzymatic degradation, and variable absorption across patients [32]. These limitations may reduce reproducibility and complicate dose optimization.

Fourth, toxicity and safety remain central concerns. Nanomaterials may induce local or systemic toxicity depending on composition, degradation profile, and exposure duration. In addition, BBB-opening strategies such as focused ultrasound or chemical disruption may improve drug access but can also compromise barrier integrity and increase the risk of neuroinflammation or unwanted entry of circulating substances [31, 33].

Finally, the field lacks standardized translational frameworks. Differences in animal models, *in vitro* BBB systems, analytical methods, and endpoint selection limit cross-study comparability and make regulatory evaluation difficult [31, 33]. For this reason, clinically relevant models, standardized biodistribution studies, long-term safety assessment, and manufacturing under good manufacturing practice conditions will be essential for future development.

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Conclusion

Brain bioavailability results from the dynamic balance between:

- Structural and functional properties of the BBB
- Efflux transporter activity
- Physicochemical characteristics of the drug molecule
- Formulation design and delivery strategy

Continued integration of nanotechnology, molecular targeting, and translational pharmacology is expected to significantly improve therapeutic outcomes in CNS disorders. Although preclinical studies have demonstrated the potential of intranasal, nanotechnology-based, and targeted delivery systems to improve brain drug exposure, clinical translation remains limited. Future studies should focus on clinically relevant models, standardized pharmacokinetic and biodistribution methods, long-term safety, scalable manufacturing, and well-designed clinical trials to determine whether these approaches can provide meaningful therapeutic benefits in patients.

Conflict of Interest

The author declares no conflict of interest.

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Author Contributions

Conceptualization, writing, analysis, and manuscript preparation were performed by the author.

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