International Conference on Biology & Earth Sciences
هفتمین همایش بین المللی زیست شناسی و علوم زمین

The blood-brain barrier: obstacles and solutions in drug delivery to the central nervous system

Sara Abdolrahmani[1], Sabra Fouladi[2], Seyedeh Zahra Bakhti [*3]

1. Collegian, Department of Biology, Faculty of Natural Sciences, University of Tabriz, Tabriz, Iran
Collegian, Department of Biology, Faculty of Natural Sciences, University of Tabriz, Tabriz, Iran
Assistant Professor, Department of Biology, Faculty of Natural Sciences, University of Tabriz, Tabriz

Abstract

Since most therapeutic agents cannot penetrate the blood-brain barrier (BBB), this poses a considerable challenge to effectively treating central nervous system (CNS) disorders. Consequently, numerous drugs demonstrate poor targeting of the brain, resulting in diminished therapeutic efficacy and heightened side effects from off-target buildup. Recent progress in materials science, nanotech, and biomaterials presents innovative methods for addressing this challenge and improving CNS drug delivery effectiveness. This review investigates the physiological composition and functions of the different cells within the BBB, along with novel approaches to improve drug permeability, including ligand conjugation, intranasal delivery, passive transcytosis, and stimulus-induced disruption. By analyzing recent studies, we highlight the main challenges and opportunities in the future development of brain-targeted drug delivery systems. Our primary goal is to improve knowledge about methods to optimize drug delivery across the blood-brain barrier, facilitating the creation of more effective therapies for central nervous system conditions.

Keywords: BBB, CNS, Nanoparticles, Targeted Therapy, Nanomedicine

1. Introduction

The blood-brain barrier (BBB) notably limits drug delivery to the brain, posing challenges for treating central nervous system (CNS) disorders such as Alzheimer's, Parkinson's, multiple sclerosis, epilepsy, and brain tumors [1, 2]. Despite its protective function, the BBB restricts the effectiveness of most drugs by preventing their passage into the brain [3, 4]. While some drugs can cross the BBB through passive diffusion, others require active transport, often hindered by molecular size and lipophilicity [5, 6]. Drugs with molecular weights above 400-500 Da generally cannot pass through, and the lipophilicity of a compound plays a critical role in its ability to penetrate the barrier [۱].

The BBB's tight structure, formed by endothelial cells, astrocytes, and pericytes, prevents the passage of most substances [3, 7]. Tight junctions between the cells limit small molecules, requiring specialized transport mechanisms for nutrients and larger molecules to enter. These mechanisms include receptor-mediated endocytosis and transporter-mediated transcytosis [۸]. However, the BBB's protective nature also prevents the brain uptake of many therapeutic drugs, which remain inaccessible despite their potential efficacy [6].

Alternative methods, such as intranasal delivery and nanotechnology, are being explored to bypass the BBB and deliver drugs directly to the brain [9]. Intranasal delivery is effective in targeting the brain through the olfactory and trigeminal pathways, reducing side effects and systemic exposure [5, 10].

In summary, while the BBB presents a major obstacle in the treatment of CNS disorders, emerging technologies such as intranasal drug delivery and nanomedicine are paving the way for more effective and targeted therapies [9]. However, overcoming the complexities of BBB permeability requires ongoing innovation and a deeper understanding of the mechanisms involved [3].

2. Blood-Brain Barrier (BBB) Structure and Function

The BBB, a dynamic, multicellular, semi-permeable membrane, first recognized by Paul Ehrlich and later confirmed by Edwin Goldman, maintains central nervous system homeostasis while restricting drug entry for neurological therapies [1]. The BBB is a crucial target for drug delivery, since capillaries are key BBB sites, and neurons are located no more than 25 μm from them [1, 7]. Pericytes, astrocytes, endothelial cells, and junctional complexes (tight and adherents' junctions) all contribute to the integrity of the BBB (Figure 1) [3].

Endothelial cells, which line cerebral blood vessels and form the core of the BBB, differ from peripheral endothelial cells in both structure and function [6]. They require more energy for transport because they contain a high mitochondrial content, lack fenestrations, and are firmly connected through adherents and tight junctions [3, 7]. Leukocyte adhesion is limited by their negative surface charge, which repels other negatively charged molecules [11]. Additionally, they contribute to the selective permeability of the BBB by maintaining high transendothelial electrical resistance (TEER) and regulating molecular transport through specialized transporters [8].

Astrocytes, or astroglia, are the most abundant glial cells, exhibiting complex and heterogeneous morphology [5]. They are classified into protoplasmic astrocytes (found in vascularized gray matter) and fibrous astrocytes (located in less vascularized white matter) [3, 6]. Their end feet interact with the basement membrane through proteins such as aquaporin-4 (AQP4) and dystroglycanopathy [4]. Astrocytes play key roles in waste clearance, blood flow regulation, ion homeostasis, and neuroimmune responses [2]. While their precise role in BBB function remains debated, they coordinate with pericytes to regulate endothelial cells and act as an interface between neurons and blood vessels [3, 8].

Pericytes are mural cells embedded within the basement membrane along capillary walls, covering nearly 100% of the CNS endothelium [1]. They are essential for neurovascular unit function and maintain close communication with endothelial cells, primarily through platelet-derived growth factor-B (PDGF-B) signaling [6, 9]. Endothelial cells secrete PDGF-B, which binds to PDGFR-β receptors on pericytes, recruiting them to blood vessels [4]. In return, pericytes regulate endothelial cells by influencing tight junction formation and astrocyte polarization [3]. A reduction in pericytes leads to a decrease in tight junctions, increasing BBB permeability [11]. Additionally, pericytes contribute to cerebral blood flow regulation, vascular development, and neuroinflammation control [1].

Adherents' junctions support BBB structural integrity and assist in assembling tight junction proteins [5]. They consist of vascular endothelial-cadherin, catenin , p120, and lipoproteins, which link endothelial cells and anchor junctional complexes to the cytoskeleton [6]. Vascular

endothelial-cadherin facilitates cell-to-cell adhesion by connecting with neighboring endothelial cells [3]. Catenin , p120, and glycoproteins act as scaffolds, bridging adherents and tight junction proteins to the cytoskeleton [7]. Other molecules, including platelet endothelial cell adhesion molecule-1 (PECAM-1), CD99, and nexins, may also contribute to adherent's junction function [8, 9]. Any alteration in adherents' junctions can compromise BBB integrity, affecting its permeability, and selectivity [1].

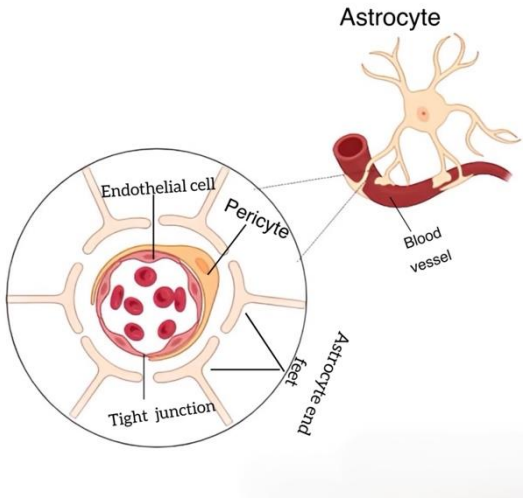

Figure 1: Endothelial cells, tight junctions, pericytes, and astrocyte end-feet are visible in the BBB.

3. The Blood-Brain Barrier and Neurodegenerative Diseases

Neurodegenerative diseases (NDs) are a large group of neurological disorders with various clinical and pathological presentations that specifically affect subsets of neurons within different functional anatomical systems [3]. These diseases, whose origins remain largely unknown, progress steadily over time [2]. Despite the identification of hundreds of NDs, diagnosing and treating them is extremely challenging due to the overlap of clinical and pathological features [4]. The number of patients suffering from debilitating CNS disorders continues to rise, even with extensive research efforts [7]. Unfortunately, there is no known cure for neurodegeneration; current treatments mainly alleviate symptoms without halting disease progression, and they often come with unanticipated side effects [8].

The development of effective preventive or protective therapies is hindered by our incomplete understanding of the mechanisms of neuronal death in NDs and the challenge of delivering therapeutic agents across the BBB into the CNS [1]. The blood-brain barrier, along with other protective barriers like the blood-cerebrospinal fluid barrier (CSFB) and the blood-retinal barrier, prevents the entry of pathogens, neurotoxins, and circulating blood cells into the CNS. These barriers also limit the efficacy of available therapeutic approaches [6].

Many currently available drugs are ineffective for treating CNS disorders because they cannot cross the BBB efficiently and maintain therapeutic concentrations in the brain [10]. Clinical failure of potentially effective treatments often stems from inadequate drug delivery techniques, rather than a lack of drug potency [11]. This remains a major challenge in neurotherapeutics [9]. As systemic administration cannot achieve sufficient drug concentrations in the brain, many promising drug candidates have been abandoned [2].

Substances can cross the BBB through several pathways under normal physiological conditions, including: i) Diffusion via transcellular lipophilia, ii) Transport via proteins and paracellular transport (through tight junctions), iii) Adsorptive transcytosis and receptor-mediated endocytosis [4]. To enhance CNS drug delivery, these transport pathways have been actively researched [1]. New strategies are being developed to address the limitations of traditional drug delivery mechanisms [5]. One promising approach involves temporarily disrupting the BBB to enable drug penetration [6]. Nanomedicine-based drug delivery systems provide a novel solution to overcoming CNS-related barriers [9]. These systems improve targeted drug delivery, pharmacokinetics, and drug bioavailability [7]. Various nanoformulations, including metal nanostructures, extracellular vesicles, liposomes, red blood cell membranes, and organic, inorganic, polymeric, and carbon-based materials, have been approved or are in clinical trials [11]. These methods leverage cellular and molecular targeting to enhance specificity, safety, and effectiveness [10].

4. Methods for Using Nanomaterials to Cross the Blood-Brain Barrier (BBB)

The treatment of neurodegenerative diseases (NDs), including Parkinson's disease (PD) and Alzheimer's disease (AD), is often complicated by the BBB, which prevents many therapeutic agents from reaching the brain [3]. To address this issue, researchers have developed nanocarrier-driven drug delivery systems that enhance drug transit across the blood-brain barrier [1]. Nanomedicines offer targeted drug delivery, improved pharmacokinetics and biodistribution, reduced metabolic clearance and side effects, and lower treatment costs due to their nanoscale size and distinct physicochemical characteristics, such as reactivity, stability, solubility, surface area, and sensitivity [7].

Inorganic nanoparticles (NPs) have shown significant promise in drug delivery, bioimaging, and biosensing for CNS-related applications [9]. Nanomaterial-based strategies for crossing the BBB can be categorized into three main approaches based on their mechanisms of action: a) Non-invasive techniques that exploit natural transport mechanisms, b) Invasive techniques (chemically or physically disrupting the BBB, c) Alternative drug delivery methods (using peripheral pathways to bypass the BBB) [6].

4.1 Non-Invasive Methods

Non-invasive techniques minimize tissue damage and systemic side effects by utilizing endogenous cellular mechanisms to transfer drugs across the BBB (Figure 2) [4].

4.1.1 Transcytosis in Passivity

Non-specific transport, also known as passive transcytosis, occurs through two primary pathways: paracellular pathway, and transcellular route [8].

Paracellular Pathway: normally, tight junctions prevent ions, polar solutes, and macromolecules from passing through endothelial cells. However, in certain brain disorders, the integrity of the BBB is compromised, allowing small and soluble molecules to pass through [7]. Downregulating tight junction proteins is one way to exploit this pathway [11]. For instance, the potassium channel modulator minoxidil sulfate (MS) can increase BBB permeability by disrupting tight junctions [2]. CTX-mHph2-III-62% nanoparticles: which co-encapsulate minoxidil, lexis can, and NECA, were developed by Zhou et al. These

nanoparticles, specifically engineered to target brain tumors, increase drug penetration by locally releasing BBB modulators [3]. M@H-NPs: a hyaluronic acid-based nanocarrier for brain metastases, was engineered by Han et al. These nanoparticles increase drug uptake in brain metastatic tumor cells (BMTCs) by targeting the CD44 receptor, which is overexpressed in breast cancer [5].

Transcellular Route: this pathway is more effective for BBB penetration as it allows direct intracellular transport via carrier-mediated and receptor-mediated transcytosis [1]. It is commonly used for transporting cationic amino acids and lipophilic carriers [6]. Allan et al. successfully used liposomal nanoparticles (HSPC: CHOL: DSPE-PEG2000) to deliver drugs for intracerebral hemorrhage (ICH). The particles accumulated at lesion sites via self-diffusion [9]. Gu et al. modified OX26 antibodies on PEGylated cationic lipid nanoparticles (OX26-PEG-CSLN) to deliver the neuroprotective agent baicalin across the BBB. These nanoparticles not only facilitated drug transport but also helped regulate extracellular amino acid levels [8]. Despite its advantages, passive transcytosis is limited to small hydrophilic compounds (less than 150 Da) and highly hydrophobic molecules (less than 400–600 Da) [7]. Consequently, additional strategies, such as temporarily increasing BBB permeability, may be required for large-molecule therapeutics [11].

4.1.2 Delivery of Drugs Intranasally

Intranasal drug delivery is a non-invasive and effective technique that enables direct transport of drugs from the nose to the brain, bypassing systemic circulation and first-pass metabolism [5].

A) Brain-to-Nose Pathways: Intranasal drug transport occurs through three primary pathways. (i) The fastest and shortest route, from the olfactory nerve to the olfactory bulb, and then to the brain [1]. (ii) Direct neuronal transport from the trigeminal nerve to the brain [2]. (iii) Indirect and less effective pathway: respiratory/gastrointestinal tract → systemic circulation → brain [7].

The fastest and most direct pathway is pathway (i), which delivers drugs to the brain through olfactory epithelial cells within 1.5–6 hours, and in some cases, within minutes [9].

The trigeminal nerve, which runs directly from the nasal cavity to the brainstem and olfactory bulb, makes pathway (ii) also effective for drug transport [6]. Pathway (iii) is the least effective because it involves systemic circulation, leading to drug metabolism and clearance [3].

B) Systems for Intranasal Drug Delivery: To prevent peripheral exposure, Uchegbu et al., developed LENK-loaded nano-peptides (30–60 nm) that effectively delivered leucine-enkephalin hydrochloride (LENK) to the olfactory bulb, thalamus, and cortex [12]. To enhance siRNA delivery to the brain, Seta et al. created MPEG-PCL-Tat nano-micelles functionalized with HIV-derived cell-penetrating peptides (Tat) [11].

Despite its advantages, intranasal delivery faces challenges that can reduce drug bioavailability, including pharyngeal drainage, mucociliary clearance, and anatomical variations in the nasal cavity [2]. Additionally, this method is less reliable due to conditions such as colds or allergies, which may affect the absorption efficiency [4].

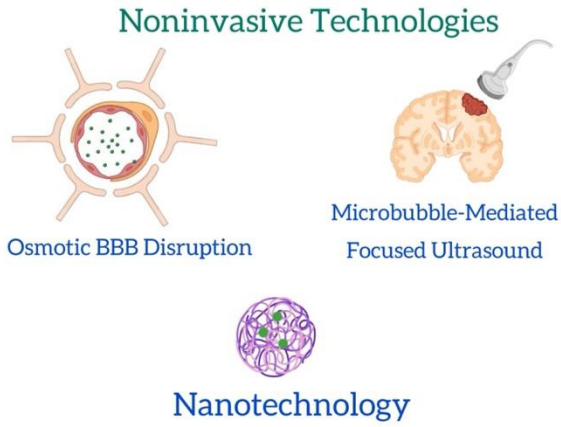

Figure 2: The picture illustrates non-invasive methods of delivering medications over the BBB. These techniques include drug carriers based on nanotechnology, targeted ultrasound-mediated by microbubbles, and osmotic BBB rupture. These methods are prospective treatments for brain tumors and neurological disorders because they seek to increase therapeutic agents' penetration into the central nervous system while reducing invasiveness.

4.2 Invasive Techniques

Invasive methods disrupt the BBB either physically or chemically to facilitate drug delivery (Figure 3) [1]. These include: convection-enhanced delivery, intraventricular, intrathecal, interstitial delivery, intracerebral implants, biochemical techniques, osmotic BBB disruption (BBBD), and ultrasound-mediated BBBD [9]. These methods aim to reduce endothelial cell integrity and break tight junctions, allowing drugs to pass by using hyperosmotic solutions, focused ultrasound, or magnetic fields [7]. However, brief openings of the BBB may allow toxins and inflammatory molecules to enter the central nervous system unintentionally, presenting potential risks [6].

4.3 Using Ligand-Conjugation to Target the Brain

Ligand-conjugated nanocarriers enhance the efficiency of BBB transport by actively targeting brain endothelial receptors [11].

4.3.1 Targeting Mediated by Transferrin Receptors

Ramalho et al. designed PLGA nanoparticles conjugated with transferrin and an anti-nesting antibody for targeted drug delivery to glioblastoma [13]. Qi et al. modified long-circulating liposomes with RI7217 monoclonal antibodies, which successfully crossed the blood-brain barrier and demonstrated anti-tumor activity [14]. To enhance brain targeting and extend circulation, Xie et al. developed dual-functional liposomes conjugated with transferrin and cell-penetrating peptides (CPPs) [15].

Nanotechnology offers innovative approaches to overcoming BBB limitations and improving drug delivery for CNS disorders [2]. Although non-invasive techniques like intranasal delivery and passive transcytosis show promise, they require further refinement [1]. Ligand-based targeting and invasive techniques provide accurate but complex solutions to enhance CNS drug penetration [7]. Future research should focus on refining these methods to ensure safety, efficacy, and clinical applicability [9].

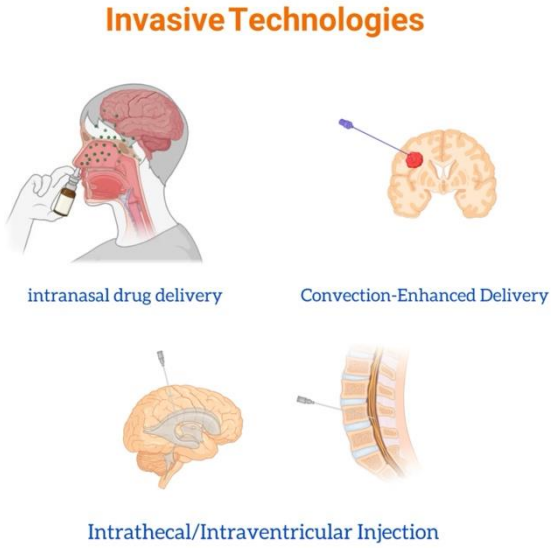

Figure 3: The picture shows invasive drug delivery technologies for the central nervous system. Convection-enhanced delivery (CED) for targeted brain drug administration, intrathecal/intraventricular injection, and intranasal drug delivery are some of these techniques. Each strategy aims to enhance the efficacy of pharmaceutical therapies, particularly for neurological conditions and brain tumors.

5. Conclusion and Prospects for the Future

Due to the protective physiological barriers of the brain, therapeutic delivery to the central nervous system (CNS) remains challenging [3]. Although drug delivery technologies have advanced significantly, low transport efficiency, safety concerns, and the complexity of CNS disorders still hinder their clinical translation [2]. New biomaterials, sophisticated nanocarriers, and precision-targeting techniques that can improve drug penetration, reduce side effects, and adapt to the evolving nature of oncologic and neurodegenerative diseases are needed to address these challenges [5]. Looking ahead, there is significant potential for transforming CNS drug delivery through the integration of artificial intelligence, personalized medicine, and minimally invasive techniques [10]. While non-invasive techniques, such as focused ultrasound and intranasal delivery, may offer safer and more efficient treatment routes [7], computational modeling and machine learning could optimize medication formulations and predict patient-specific responses [8]. Ultimately, a multidisciplinary approach combining knowledge from neuroscience, material science, pharmacology, and biomedical engineering is essential to overcoming the obstacles in CNS drug delivery [11]. The future of CNS therapeutics could evolve from having limited treatment options to offering truly targeted, effective, and patient-specific therapies [15]. With sustained innovation and collaboration, people suffering from debilitating neurological disorders may have new hope [6].

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