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THE BLOOD–BRAIN BARRIER: STRUCTURE, FUNCTIONS, AND MECHANISMS OF DYSFUNCTION IN CENTRAL NERVOUS SYSTEM DISEASES

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Abstract

The blood–brain barrier (BBB) is a specialized neurovascular interface that maintains central nervous system homeostasis by regulating the exchange of substances between the circulation and brain. It is a dynamic component of the neurovascular unit (NVU), comprising brain endothelial cells, tight and adherens junctions, pericytes, astrocytic end-feet, and the extracellular matrix. BBB permeability is determined by passive diffusion, carrier-mediated transport, receptor-mediated transcytosis, and active efflux systems. BBB disruption involves endothelial dysfunction, tight junction degradation, oxidative stress, inflammation, matrix metalloproteinase activation, and NVU dysfunction, contributing to disorders such as ischemic stroke, multiple sclerosis, Alzheimer’s disease, Parkinson’s disease, amyotrophic lateral sclerosis, and brain tumors. The BBB also remains a major obstacle to CNS drug delivery. Emerging approaches, including receptor-mediated delivery, nanoparticles, and focused ultrasound, aim to improve drug penetration while preserving barrier integrity.

Keywords: Blood-brain barrier, neurovascular unit, endothelial cells, tight junctions, BBB dysfunction, neurodegenerative diseases, CNS drug delivery.

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Introduction

The blood–brain barrier (BBB) is a highly selective, semipermeable physiological border that separates the circulating systemic blood from the brain and extracellular fluid in the central nervous system (CNS). Unlike peripheral capillaries, which permit relatively free exchange of solutes and ions, the BBB serves as a formidable gatekeeper, strictly regulating the movement of molecules into and out of the neural parenchyma. This rigorous regulation is essential for maintaining CNS homeostasis. Because neuronal signaling depends heavily on precise gradients of ions—particularly potassium, sodium, and calcium—and relies on neurotransmitters that also circulate in the peripheral blood (such as glutamate and glycine), any unregulated influx of systemic fluids would result in profound excitotoxicity and neuronal depolarization (Daneman and Prat, 2015). Furthermore, the brain requires an isolated environment to protect its limited regenerative capacity from circulating neurotoxins, systemic pathogens, and potentially damaging immune responses.

Historically viewed merely as an impermeable physical wall, the BBB is now understood to be a highly dynamic and interactive structural complex. This paradigm shift gave rise to the concept of the neurovascular unit (NVU), which posits that BBB function does not rely solely on the intrinsic properties of endothelial cells, but depends heavily on coordinated interactions between brain microvascular endothelial cells, pericytes, astrocytic end-feet, microglia, neurons, and the extracellular matrix (ECM) (Hawkins and Davis, 2005; Iadecola, 2017). Dysfunction within this complex network is a critical pathophysiological mechanism in numerous CNS disorders, including ischemic stroke, neurodegenerative diseases, and neuroinflammation. Consequently, preserving or restoring NVU integrity has emerged as a major therapeutic objective.

The purpose of this review is to synthesize current evidence regarding the structural organization, physiological functions, transport mechanisms, and pathological alterations of the BBB, highlighting its central role in the pathogenesis and potential treatment of CNS diseases.

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2. Anatomical and Cellular Structure of the Blood–Brain Barrier

2.1 Brain microvascular endothelial cells

The anatomical core of the BBB is formed by specialized brain microvascular endothelial cells (BMECs). Compared to peripheral endothelium, BMECs exhibit a distinct morphological and functional phenotype characterized by the absence of fenestrations, a significantly reduced rate of pinocytosis and transcytosis, and an exceptionally high transendothelial electrical resistance (TEER), often exceeding 1000 $\Omega \cdot cm^2$ in vivo (Abbott et al., 2010). This high TEER fundamentally restricts the paracellular diffusion of water-soluble agents. Furthermore, BMECs feature highly polarized luminal (blood-facing) and abluminal (brain-facing) membranes, each expressing a distinct repertoire of transport proteins and ion channels (O'Brown et al., 2018). The luminal surface is coated with the endothelial glycocalyx—a network of membrane-bound proteoglycans and glycoproteins that repels negatively charged molecules and regulates blood cell adhesion.

2.2 Tight junctions and adherens junctions

The restriction of paracellular movement across the BBB is orchestrated by highly specialized junctional complexes: tight junctions (TJs) and adherens junctions (AJs). TJs form the primary seal between adjacent endothelial cells. The molecular architecture of TJs includes transmembrane proteins such as claudins, occludin, and junctional adhesion molecules (JAMs). Claudin-5 is particularly crucial; it is the most highly expressed TJ protein at the BBB. Deletion of claudin-5 in murine models results in a size-selective loosening of the barrier, permitting the influx of molecules under 800 Daltons and leading to early postnatal mortality, thereby confirming its indispensable role in paracellular gating (Nitta et al., 2003). These transmembrane proteins are anchored to the actin cytoskeleton via intracellular scaffolding proteins, most notably zonula occludens-1 and -2 (ZO-1, ZO-2). Adjacent to TJs are AJs, which primarily provide structural support and intercellular adhesion. Mediated mainly by vascular endothelial cadherin (VE-cadherin) and linked to the cytoskeleton via catenins, AJs are critical for the initial assembly of the BBB and the subsequent maturation of TJs (O'Brown et al., 2018).

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2.3 Pericytes

Pericytes are mural cells embedded within the endothelial basement membrane. The CNS vasculature possesses the highest pericyte-to-endothelial cell ratio in the body, underscoring their importance in brain homeostasis. Pericytes physically interact with BMECs through peg-and-socket contacts, facilitating direct gap junctional communication and reciprocal paracrine signaling, notably via the PDGF-B/PDGFRβ and TGF-β signaling pathways (Armulik et al., 2010). They play an essential role in BBB induction during embryogenesis, regulate the expression of tight junction proteins, and inhibit the expression of leukocyte adhesion molecules on endothelial cells. Furthermore, pericytes possess contractile properties, allowing them to regulate capillary diameter and contribute to neurovascular coupling—the process linking neuronal demand to regional cerebral blood flow. Pericyte loss or dysfunction severely compromises capillary stability and leads to increased BBB permeability, a hallmark of aging and neurodegenerative decline (Bell et al., 2010).

2.4 Astrocytic end-feet

Astrocytes provide the crucial cellular link between the vasculature and neuronal synapses. Their specialized processes, termed end-feet, almost entirely ensheathe the cerebral microvasculature. Astrocytes are responsible for secreting factors (such as sonic hedgehog and retinoic acid) that induce and maintain the barrier phenotype in BMECs (Abbott et al., 2006). The end-feet are heavily polarized and express high concentrations of specific channels facing the basal lamina, most importantly the water channel aquaporin-4 (AQP4) and the inwardly rectifying potassium channel Kir4.1.

This precise molecular arrangement allows astrocytes to strictly regulate water volume and buffer the extracellular potassium generated during intense neuronal activity, thus preventing excitotoxicity. Additionally, astrocytes relay metabolic signals from active neurons to the vasculature, forming the physiological basis of functional hyperemia.

2.5 Basement membrane and extracellular matrix

The cellular components of the NVU are supported by a complex extracellular matrix known as the basement membrane, which is conceptually divided into an

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inner vascular layer (produced by ECs and pericytes) and an outer parenchymal layer (produced by astrocytes). The ECM is composed primarily of specific isoforms of laminins, collagen type IV, nidogen, and heparan sulfate proteoglycans (Zhao et al., 2015). The basement membrane is not merely a passive structural scaffold; it actively regulates cellular phenotypes. For instance, binding of endothelial integrins to ECM laminins is necessary to maintain proper tight junction localization. Disruption of this matrix, particularly by matrix metalloproteinases (MMPs) during pathological states, leads directly to BBB breakdown (Yang and Rosenberg, 2015).

3. Physiological Functions of the Blood–Brain Barrier

The BBB is a dynamic regulatory interface rather than a static wall. Its most fundamental physiological function is the regulation of CNS homeostasis. By enforcing selective permeability, the BBB shields the brain from fluctuations in systemic hormones, inflammatory mediators, and diet-derived neuroactive substances, while protecting against circulating neurotoxins and pathogens (Keaney and Campbell, 2015). Concurrently, it tightly regulates the concentration of ions (Na+, K+, Ca2+) to maintain the optimal microenvironment for action potential propagation.

Beyond protection, the BBB serves as the brain's primary logistical hub. It facilitates the massive influx of essential nutrients, primarily glucose and amino acids, required to meet the high metabolic demands of neural tissue. Conversely, it mediates the clearance of metabolic waste products and neurotoxic byproducts—such as amyloid-β (Aβ)—from the brain parenchyma into the systemic circulation (Tarasoff-Conway et al., 2015). Furthermore, while the CNS was traditionally considered "immune privileged," recent research clarifies that the BBB actively coordinates immune surveillance. In healthy states, it restricts the entry of naive leukocytes while allowing a controlled trafficking of activated T cells, thereby maintaining immune defense without provoking destructive neuroinflammation (Engelhardt et al., 2017).

4. Molecular Mechanisms of Transport Across the BBB

The restriction of paracellular flux dictates that molecules must utilize transcellular pathways to cross the BBB. These transport mechanisms are strictly organized.

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4.1 Passive diffusion

Passive diffusion across the lipid bilayers of BMECs is restricted primarily to small (typically <400 Daltons), highly lipophilic, and uncharged molecules. Essential blood gases (O2 and CO2) diffuse freely to support oxidative metabolism. However, for most pharmacological agents, high lipid solubility does not guarantee CNS entry, as many lipophilic compounds are rapidly intercepted by endothelial efflux pumps (Pardridge, 2012).

4.2 Carrier-mediated transport

To acquire hydrophilic nutrients, BMECs employ carrier-mediated transport (CMT) systems. These solute carriers (SLCs) transport specific substrates down their concentration gradients. The most prominent is the glucose transporter 1 (GLUT1), heavily expressed on both luminal and abluminal membranes, ensuring a continuous supply of glucose to the brain. Other vital carriers include the large neutral amino acid transporter 1 (LAT1), which transports essential amino acids (such as leucine and phenylalanine) as well as the drug L-DOPA, and monocarboxylate transporters (MCT1) for lactate and ketones (Zhao et al., 2015).

4.3 Receptor-mediated transcytosis

Large macromolecules, such as peptides and proteins, traverse the BBB via receptor-mediated transcytosis (RMT). The target molecule binds to a specific receptor on the luminal membrane, triggering endocytosis into a clathrin-coated vesicle, transport across the endothelial cytoplasm, and exocytosis at the abluminal membrane. Classic examples include the transferrin receptor, which mediates iron transport, and the insulin receptor (Thomsen et al., 2017; Ayloo and Gu, 2019). The RMT pathway has become a major target for designing CNS drug delivery vectors.

4.4 Efflux transport

A defining characteristic of the BBB is the robust expression of ATP-binding cassette (ABC) efflux transporters on the luminal membrane. The most critical are P-glycoprotein (P-gp/ABCB1) and Breast Cancer Resistance Protein (BCRP/ABCG2), along with multidrug resistance-associated proteins (MRPs). These pumps actively extrude a vast array of structurally diverse, lipophilic

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xenobiotics and metabolic waste products back into the bloodstream (Löscher and Potschka, 2005). Efflux transport is a major obstacle in CNS pharmacotherapy, as it actively restricts the brain penetration of most antibiotics, chemotherapeutics, and antiepileptic drugs.

5. Mechanisms of Blood–Brain Barrier Dysfunction

Loss of BBB integrity is a common denominator in numerous neurological disorders. Barrier dysfunction is typically driven by a convergence of tight junction degradation, direct endothelial injury, and the loss of neurovascular supporting cells.

Pathologically, BBB breakdown involves distinct mechanisms regarding transcellular versus paracellular leak. Classic studies using electron microscopy and tracer molecules have demonstrated that during the early stages of diseases like stroke, barrier failure often begins with increased vesicular transcytosis (transcellular pathway) prior to the physical disassembly of tight junctions (paracellular pathway) (Knowland et al., 2014). As the pathology progresses, oxidative stress (reactive oxygen and nitrogen species) and inflammatory cytokines (e.g., TNF-α, IL-1β) activate matrix metalloproteinases (especially MMP-2 and MMP-9) (Yang and Rosenberg, 2015). These proteases cleave tight junction proteins and degrade the basement membrane ECM, leading to frank paracellular disruption.

Dysfunction in other NVU components exacerbates this breakdown. Pericyte detachment reduces endothelial survival and vascular stability. Astrocytic dysfunction, characterized by the retraction of end-feet and loss of polarized AQP4 expression, impairs water regulation and exacerbates edema (Abbott et al., 2006). Moreover, damage to the endothelial glycocalyx exposes adhesion molecules, facilitating uncontrolled leukocyte adhesion and diapedesis.

The consequences of BBB dysfunction are severe. Increased permeability leads to the extravasation of plasma proteins (e.g., albumin, fibrinogen) into the brain parenchyma. Fibrinogen leakage activates microglia and drives neuroinflammation (Sweeney et al., 2018). Furthermore, osmotically driven water accumulation results in vasogenic edema, raising intracranial pressure. The entry of blood-borne neurotoxins and the dysregulation of local ion

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concentrations collectively precipitate secondary neuronal injury and cell death (Zlokovic, 2008).

6. BBB Dysfunction in Central Nervous System Diseases

6.1 Ischemic stroke

In ischemic stroke, the sudden cessation of blood flow induces severe hypoxia, triggering an early surge of reactive oxygen species and inflammatory signaling. Endothelial energy failure leads to the immediate upregulation of transcytosis, followed swiftly by the activation of MMPs that digest claudin-5 and the basal lamina (Knowland et al., 2014). This paracellular failure results in massive vasogenic edema. Critically, severe BBB disruption renders the ischemic brain susceptible to hemorrhagic transformation—especially following delayed reperfusion therapy—where the structural collapse of the microvasculature allows blood to extravasate into the fragile infarcted tissue (Jiang et al., 2018).

6.2 Multiple sclerosis and neuroinflammatory disorders

Multiple sclerosis (MS) is driven by autoimmune demyelination, but early BBB dysfunction is a prerequisite for disease progression. In MS, local or systemic inflammatory cytokines induce endothelial activation, upregulating the expression of adhesion molecules like VCAM-1 and ICAM-1. This allows autoreactive T lymphocytes and macrophages to firmly adhere and transmigrate into the CNS across the paracellular space (Lécuyer et al., 2016). The ensuing inflammatory cascade further degrades tight junctions, causing a localized BBB leakiness that can be visualized as gadolinium-enhancing lesions on clinical MRI.

6.3 Alzheimer's disease

BBB dysfunction in Alzheimer's disease (AD) is increasingly recognized as both a consequence and a primary driver of pathogenesis. Post-mortem and advanced imaging studies reveal early, progressive pericyte degeneration in AD, which correlates with BBB leakiness well before significant cognitive decline (Montagne et al., 2015). The BBB typically clears neurotoxic Aβ from the brain via the efflux transporter LRP1; however, in AD, LRP1 expression is diminished, while the influx receptor RAGE is upregulated, leading to a net accumulation of Aβ (Tarasoff-Conway et al., 2015). The leaked plasma proteins (like fibrinogen)

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combined with Aβ toxicity sustain a chronic neuroinflammatory state, accelerating tau pathology and neuronal loss (Sweeney et al., 2019).

6.4 Parkinson's disease and other neurodegenerative diseases

Evidence points to similar microvascular pathology in Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). In PD, the aggregation of alpha-synuclein has been shown to induce endothelial dysfunction and pericyte loss, promoting local barrier leakiness and microgliosis (Sweeney et al., 2018). Similarly, in ALS, capillary ultrastructural abnormalities and reduced tight junction expression in the spinal cord and motor cortex suggest that NVU breakdown contributes to the microenvironmental toxicity that destroys motor neurons.

6.5 Brain tumors

In primary brain tumors like glioblastoma, as well as metastatic CNS lesions, tumor-driven hypoxia stimulates pathological angiogenesis via massive secretion of VEGF. The newly formed tumor vasculature is morphologically abnormal, lacking proper astrocytic coverage and exhibiting diminished tight junction integrity. This creates the so-called blood-tumor barrier (BTB), which is notoriously heterogeneous—while some areas are leaky, contributing to severe peritumoral edema, other invasive margins retain intact BBB properties, successfully shielding tumor cells from systemic chemotherapeutics (Arvanitis et al., 2020).

7. Clinical and Therapeutic Implications

The BBB represents a profound therapeutic paradox: its formidable barrier properties protect the brain from toxins, yet simultaneously prevent over 98% of small-molecule drugs and nearly 100% of large-molecule therapeutics (e.g., monoclonal antibodies, gene therapies) from reaching CNS targets (Pardridge, 2012). This represents the primary bottleneck in neuropharmacology.

To overcome this, several innovative delivery strategies are being intensely investigated. The "Trojan horse" approach utilizes receptor-mediated transcytosis by conjugating drugs or liposomes to antibodies against the transferrin or insulin receptors, thereby tricking the BBB into transporting the therapeutic payload into

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the brain (Dong, 2018). Nanoparticle-based approaches aim to shield drugs from efflux pumps while facilitating cellular uptake through specific surface functionalization. Furthermore, MRI-guided focused ultrasound (FUS), combined with intravenous microbubbles, is being utilized clinically to temporarily and safely open tight junctions in targeted brain regions. This reversible opening provides a transient window for drug delivery and is currently in clinical trials for AD and glioblastoma (Lipsman et al., 2018).

8. Current Challenges and Future Perspectives

Despite significant advancements, several challenges remain. Recent single-cell RNA sequencing (scRNA-seq) studies have illuminated the profound heterogeneity of the brain vasculature, demonstrating that BBB properties vary across the arteriovenous axis (zonation) and between different anatomical brain regions (Vanlandewijck et al., 2018). This heterogeneity complicates the development of universal BBB-targeting drugs.

Furthermore, traditional in vitro static BBB models fail to replicate the physiological shear stress of blood flow and the complex multi-cellular architecture of the NVU. There is also a recognized translational gap between murine models and human clinical physiology (Profaci et al., 2020). Future research is pivoting toward the development of sophisticated human induced pluripotent stem cell (hiPSC)-derived, microfluidic "BBB-on-a-chip" models and brain organoids. Additionally, as we appreciate the complexity of the NVU, therapeutic strategies must shift from solely targeting endothelial cells to holistic approaches aimed at restoring pericyte function, normalizing astrocytic end-feet, and stabilizing the extracellular matrix.

9. Conclusion

The blood–brain barrier is an exquisite, highly dynamic neurovascular interface essential for CNS health. Its integrity relies not on a single cell type, but on the continuous, synchronized interactions between endothelial cells, tight junctions, pericytes, astrocytes, and the extracellular matrix that collectively comprise the neurovascular unit. Dysfunction within this complex system—whether driven by acute ischemia, chronic neurodegeneration, or unchecked inflammation—precipitates a catastrophic loss of CNS homeostasis, promoting edema, immune

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cell infiltration, and neuronal death. Moving forward, acknowledging the BBB as both a primary participant in neurological disease pathology and a critical barrier to pharmacological intervention will be vital. Overcoming the challenges of CNS drug delivery and developing therapies that actively stabilize the neurovascular unit hold profound promise for the future treatment of devastating neurological disorders.

References

1. Abbott, N. J., Ronnback, L., & Hansson, E. (2006). Astrocyte-endothelial interactions at the blood-brain barrier. Nature Reviews Neuroscience, 7(1), 41-53.
2. Abbott, N. J., Patabendige, A. A., Dolman, D. E., Yusof, S. R., & Begley, D. J. (2010). Structure and function of the blood-brain barrier. Neurobiology of Disease, 37(1), 13-25.
3. Armulik, A., Genové, G., Mäe, M., Nisancioglu, M. H., Wallgard, E., Niaudet, C., ... & Betsholtz, C. (2010). Pericytes regulate the blood-brain barrier. Nature, 468(7323), 557-561.
4. Arvanitis, C. D., Ferraro, G. B., & Jain, R. K. (2020). The blood-brain barrier and blood-tumour barrier in brain tumours and metastases. Nature Reviews Cancer, 20(1), 26-41.
5. Ayloo, S., & Gu, C. (2019). Transcytosis at the blood-brain barrier. Current Opinion in Neurobiology, 57, 32-38.
6. Banks, W. A. (2016). From blood-brain barrier to blood-brain interface: new opportunities for CNS drug delivery. Nature Reviews Drug Discovery, 15(4), 275-292.
7. Bell, R. D., Winkler, E. A., Sagare, A. P., Singh, I., LaRue, B., Deane, R., & Zlokovic, B. V. (2010). Pericytes control key neurovascular functions and neuronal phenotype in the adult brain and during brain aging. Neuron, 68(3), 409-427.
8. Daneman, R., & Prat, A. (2015). The blood-brain barrier. Cold Spring Harbor Perspectives in Biology, 7(1), a020412.
9. Dong, X. (2018). Current strategies for brain drug delivery. Theranostics, 8(6), 1481-1493.

Prima Journal of Integrated Studies
ISSN (E): 3054-338X
Volume 01, Issue 06, June, 2026
Website: https://researchiapress.com

10. Engelhardt, B., Vajkoczy, P., & Weller, R. O. (2017). The movers and shapers in immune privilege of the CNS. Nature Immunology, 18(2), 123-131.
11. Hawkins, B. T., & Davis, T. P. (2005). The blood-brain barrier/neurovascular unit in health and disease. Pharmacological Reviews, 57(2), 173-185.
12. Iadecola, C. (2017). The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. Neuron, 96(1), 17-42.
13. Jiang, X., Andjelkovic, A. V., Zhu, L., Zou, T., Ding, G. L., Li, Y., ... & Keep, R. F. (2018). Blood-brain barrier dysfunction and recovery after ischemic stroke. Progress in Neurobiology, 163-164, 144-171.
14. Keaney, J., & Campbell, M. (2015). The dynamic blood-brain barrier. FEBS Journal, 282(21), 4067-4083.
15. Knowland, D., Arac, A., Sekiguchi, K. J., Hsu, M., Lutz, S. E., Perrino, J., ... & Agalliu, D. (2014). Stepwise recruitment of transcellular and paracellular pathways underlies blood-brain barrier breakdown in stroke. Neuron, 82(3), 603-617.
16. Lécuyer, M. A., Kebir, H., & Prat, A. (2016). Glial influences on BBB functions and molecular players in immune cell trafficking. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1862(3), 472-482.
17. Lipsman, N., Meng, Y., Bethune, A. J., Huang, Y., Logan, W. J., Waspe, A. C., ... & Hynynen, K. (2018). Blood-brain barrier opening in Alzheimer's disease using MR-guided focused ultrasound. Nature Communications, 9(1), 2336.
18. Löscher, W., & Potschka, H. (2005). Role of drug efflux transporters in the brain for drug disposition and treatment of brain diseases. Progress in Neurobiology, 76(1), 22-76.
19. Montagne, A., Barnes, S. R., Sweeney, M. D., Halliday, M. R., Sagare, A. P., Zhao, Z., ... & Zlokovic, B. V. (2015). Blood-brain barrier breakdown in the aging human hippocampus. Neuron, 85(2), 296-302.
20. Nitta, T., Hata, M., Gotoh, S., Seo, Y., Sasaki, H., Hashimoto, N., ... & Tsukita, S. (2003). Size-selective loosening of the blood-brain barrier in claudin-5-deficient mice. Journal of Cell Biology, 161(3), 653-660.
21. O'Brown, N. M., Pfau, S. J., & Gu, C. (2018). Establishing and maintaining the blood-brain barrier. Annual Review of Neuroscience, 41, 169-197.
22. Pardridge, W. M. (2012). Drug transport across the blood-brain barrier. Journal of Cerebral Blood Flow & Metabolism, 32(11), 1959-1972.

Prima Journal of Integrated Studies
ISSN (E): 3054-338X
Volume 01, Issue 06, June, 2026
Website: https://researchiapress.com

23. Profaci, C. P., Munji, R. N., Foulquier, S., & Daneman, R. (2020). The blood-brain barrier in health and disease: Important unanswered questions. Journal of Experimental Medicine, 217(4), e20190062.
24. Sweeney, M. D., Sagare, A. P., & Zlokovic, B. V. (2018). Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nature Reviews Neurology, 14(3), 133-150.
25. Sweeney, M. D., Zhao, Z., Montagne, A., Nelson, A. R., & Zlokovic, B. V. (2019). Blood-brain barrier: from physiology to disease and back. Physiological Reviews, 99(1), 21-78.
26. Tarasoff-Conway, J. M., Carare, R. O., Osorio, R. S., Glodzik, L., Butler, T., Fieremans, E., ... & de Leon, M. J. (2015). Clearance systems in the brain—implications for Alzheimer disease. Nature Reviews Neurology, 11(8), 457-470.
27. Thomsen, M. S., Routhe, L. J., & Moos, T. (2017). The capillary endothelial receptor for transferrin: from membrane dynamics to susceptibility for targeted drug delivery. Frontiers in Pharmacology, 8, 471.
28. Vanlandewijck, M., He, L., Mäe, M. A., Andrae, J., Ando, K., Del Gaudio, F., ... & Betsholtz, C. (2018). A molecular atlas of cell types and zonation in the brain vasculature. Nature, 554(7693), 475-480.
29. Yang, Y., & Rosenberg, G. A. (2015). Blood-brain barrier breakdown in acute and chronic cerebrovascular disease. Stroke, 46(11), 3322-3328.
30. Zhao, Z., Nelson, A. R., Betsholtz, C., & Zlokovic, B. V. (2015). Establishment and dysfunction of the blood-brain barrier. Cell, 162(5), 1064-1078.
31. Zlokovic, B. V. (2008). The blood-brain barrier in health and chronic neurodegenerative disorders. Neuron, 57(2), 178-201.