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HISTOLOGY AND HISTOPATHOLOGY

ISSN: 0213-3911
e-ISSN: 1699-5848

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DOI: 10.14670/HH-18-740
Article type: REVIEW
Accepted: 2024-04-01
Epub ahead of print: 2024-04-01

Blood-brain barrier disruption following brain injury: implications for clinical practice

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Short title: Blood-brain barrier disruption following brain injury

Abstract

The blood-brain barrier (BBB) plays a critical role in regulating the exchange of substances between peripheral blood and the central nervous system and in maintaining the stability of the neurovascular unit in neurological diseases. To guide clinical treatment and basic research on BBB protection following brain injury, this manuscript reviews how BBB disruption develops and influences neural recovery after stroke and traumatic brain injury (TBI). By summarizing the pathological mechanisms of BBB damage, we underscore the critical role of promoting BBB repair in managing brain injury. We also emphasize the potential for personalized and precise therapeutic strategies and the need for continued research and innovation. From this, broadening insights into the mechanisms of BBB disruption and repair could pave the way for breakthroughs in the treatment of brain injury-related diseases.

Keywords: blood-brain barrier, permeability, stroke, traumatic brain injury, pathological mechanisms

Introduction

The blood-brain barrier (BBB), an essential component of the central nervous system (CNS), serves as a critical interface between the brain and systemic circulation. Its primary function is to maintain the cerebral microenvironment by controlling the exchange of substances between the blood and the brain. Composed of endothelial cells (ECs), pericytes, astrocytes, neurons, and extracellular matrix (ECM), collectively known as the neurovascular unit (NVU), the BBB is characterized by selective permeability. This functionality is vital for protecting the brain from potentially harmful agents while allowing essential nutrients to pass through (Khatri et al., 2012; Banks, 2015; Sharma et al., 2022).

Disruption of the BBB following brain injuries, such as ischemic stroke and traumatic brain injury (TBI), constitutes a significant pathological event with extensive implications. This breach enables peripheral leukocytes and other immune cells to infiltrate the brain, intensifying neuroinflammation and potentially hastening the onset of neurological disorders like Parkinson's (PD) and Alzheimer's disease (AD) (Ren et al., 2019). Consequently, the integrity of the BBB is closely linked to neuronal health, and its compromise can lead to increased neuronal damage, neuroinflammation, and worsening neurological outcomes (Krueger et al., 2019; Nadareishvili et al., 2019).

Despite its crucial role in the CNS, the therapeutic options for BBB repair and protection remain limited. However, recent advancements in scientific research are shedding light on the intricate functions of the BBB and the consequences of its disruption, providing new insights for clinical applications and treatment strategies (Furtado et al., 2018). This manuscript aims to offer a comprehensive overview of the BBB's role in brain injuries, its impact on clinical

practices, and the emerging treatment options. Gaining insight into the cellular and molecular mechanisms of BBB disruption, as well as understanding the pathological effects and dynamic progression of BBB impairment following brain injury, this paper aims to underscore the BBB's significance in neurology and its potential as a target for innovative therapeutic interventions, paving the way for breakthroughs in the treatment and prevention of neurological disorders.

Pathological Mechanisms and Progression of BBB Disruption

Cellular and molecular mechanisms of BBB disruption

The disruption of the BBB is intricately linked to brain injuries, displaying a complex interplay of cellular and molecular responses. The BBB, a crucial neurovascular interface, maintains the central nervous system's homeostasis and protects it from potentially harmful substances. In the context of brain injury, several cellular components and molecular pathways are implicated in BBB disruption.

EC dysfunction

ECs are fundamental in maintaining the BBB's structural integrity. They form tight junctions (TJs), which are critical for the barrier's selective permeability. Following a brain injury, these cells are exposed to various stressors, like hypoxia and inflammation, which can compromise TJs. This disruption is not merely a passive consequence but an active process involving several molecular pathways. Pro-inflammatory cytokines and reactive oxygen species (ROS) are released as a result, further exacerbating the BBB breakdown (Nian et al., 2020). These

cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukins, can alter the expression and function of TJ proteins, leading to increased BBB permeability.

Oxidative stress

In pathological states like hypoxia, oxidative stress plays a pivotal role in BBB disruption. The TJ complexes become destabilized due to the altered cellular environment, a process primarily driven by hypoxia-inducible factor-1 (HIF-1). HIF-1 is a key regulator in response to oxygen deprivation, and its activation leads to several downstream effects, including the destabilization of TJ proteins through delocalization and tyrosine phosphorylation. This alteration in TJ integrity significantly contributes to BBB permeability changes (Engelhardt et al., 2014). Oxidative stress, characterized by excessive ROS, can damage cellular components, including lipids, proteins, and DNA, leading to EC dysfunction and death, further compromising the BBB.

Astrocyte and pericyte response

Astrocytes and pericytes are integral components of the neurovascular unit (NVU) and play crucial roles in maintaining BBB integrity. Under pathological conditions, such as those encountered post-stroke, these cells undergo functional changes. They produce excessive ROS and reactive nitrogen species (RNS), including nitric oxide (NO) and peroxynitrite ($ONOO^-$). This production of reactive species leads to the release of inflammatory mediators like TNF-α, contributing to BBB disruption and neuronal damage. Astrocytes, in particular, are also involved in neurotransmitter regulation, and their dysregulation can lead to excitotoxicity, further exacerbating the injury to the BBB and surrounding neural tissues (Ghosh et al., 2019).

Inflammatory Cascade and Immune Cell Infiltration

Cytokine and immune cell response

The inflammatory response following brain injury is a critical factor in BBB disruption. Cytokines such as TNF-α and IL-1β are released in response to injury, playing vital roles in modulating immune responses. These cytokines are not only markers of inflammation but also active participants in the pathogenesis of BBB disruption. They influence the expression of adhesion molecules on ECs, promoting the infiltration of immune cells, like monocytes, macrophages, neutrophils, and T cells, into the brain. This infiltration, while part of the body's natural defense mechanism, can exacerbate BBB damage. Immune cells release additional ROS, matrix metalloproteinase (MMP), and cytokines, creating a feedback loop that further compromises the integrity of the BBB and perpetuates the inflammatory response (Cash and Theus, 2020; Zheng et al., 2022).

Matrix metalloproteinase (MMP) activity

MMPs play a significant role in BBB disruption, especially in the context of stroke. These enzymes degrade ECM proteins and are critical in remodeling processes. In the BBB, MMPs target key components such as occludin, claudin-5, and zonula occludens-1, crucial for maintaining TJs. The activation and overexpression of MMPs, often triggered by ROS and cytokines, lead to increased BBB permeability and structural breakdown. This process not only exacerbates BBB disruption but also contributes to the progression of neuronal damage. The degradation of TJ proteins and BM components by MMPs facilitates the transmigration of

immune cells across the BBB, worsening the inflammatory response and potentially leading to further neurovascular damage (Liu et al., 2012; Greene et al., 2019; Song et al., 2020).

Interplay between cellular components and molecular signaling

The disruption of the BBB in brain injuries involves a complex interplay between various cellular components and molecular signaling pathways. ECs, astrocytes, pericytes, immune cells, and molecular mediators like cytokines, ROS, RNS, and MMPs all interact in a dynamic and interconnected manner. This interaction results in a cascade of events that destabilize the BBB, alter its permeability, and potentially lead to a range of pathological outcomes, including edema, neuronal damage, and impairment in brain function.

Progression across different phases

The progression of BBB disruption following brain injury unfolds in distinct phases, each characterized by unique pathological changes and therapeutic opportunities (Table 1). Initially, the hyperacute phase occurs within the first six hours post-injury, marked by rapid BBB damage due to sudden hypoxia, leading to increased permeability and infiltration of normally restricted substances. This early disruption necessitates immediate medical intervention to mitigate damage and influence recovery outcomes (Wu et al., 2020).

Following the hyperacute phase, the acute phase spans from 6 to 60 hours post-injury. This phase is characterized by an intense neuroinflammatory response, further increasing BBB permeability. Cytokines, especially TNF-α and IL-1β, exacerbate BBB disruption, enhancing immune cell infiltration and contributing to neurological damage (Cash and Theus, 2020; Wu

et al., 2020).

The subacute phase, lasting from one to three weeks post-injury, represents a shift toward repair and recovery. Despite elevated BBB permeability, repair processes such as neuroprotective inflammation and angiogenesis become predominant. This phase is critical for therapeutic interventions aimed at promoting repair and mitigating long-term damage (Wu et al., 2020).

Beyond six weeks post-injury, the chronic phase sees the continuous manifestation of the effects of the initial. Persistent BBB disruption contributes to ongoing inflammation and oxidative stress, impacting neural recovery and function. This phase is crucial for sustained rehabilitation and recovery strategies, focusing on reversing BBB disruption effects and fostering neural regeneration (Wu et al., 2020).

These phases highlight the evolving pathological landscape following brain injury, emphasizing the need for phase-specific therapeutic strategies to address the multifaceted nature of BBB disruption and its implications for recovery and long-term brain health.

Impacts of BBB Disruption on Neural Recovery

BBB disruption following brain injury significantly impacts neural recovery, presenting a complex challenge in both stroke and TBI. This complexity is reflected in various pathophysiological responses and their implications in the recovery process.

The disruption of the BBB allows an uncontrolled influx of immune cells, neurotoxic substances, and pro-inflammatory cytokines into the brain, intensifying neuroinflammation and contributing to neural tissue damage. This results in a cascade of inflammatory responses at the injury site, exacerbating neuronal death and dysfunction. Post-TBI, BBB dysfunction permits

proteins and immune cells to infiltrate the brain, leading to complications like edema and chronic inflammation, which can perpetuate BBB permeability issues, further exacerbating damage (Fahey and Doyle, 2019; Cash and Theus, 2020; Bodnar et al., 2021; Hu and Tao, 2021).

The compromised BBB is also intricately linked to the progression of neurodegenerative diseases like AD and PD. Increased BBB permeability facilitates the buildup of neurotoxic proteins characteristic of these diseases. Chronic neuroinflammation, stemming from BBB disruption, is believed to play a pivotal role in the development and progression of these disorders (Ren et al., 2019).

BBB disruption contributes to secondary brain injury, characterized by metabolic disturbances, oxidative stress, and EC apoptosis. Stroke-induced BBB permeability changes allow harmful substances to invade brain tissue, escalating neuronal damage. This necessitates interventions targeting oxidative stress and EC apoptosis to mitigate further damage (Choudhury and Ding, 2016; Ma et al., 2017; Goenka et al., 2019; Wang et al., 2019).

Neuroplasticity, central to recovery, is adversely affected by BBB disruption. An altered microenvironment impedes processes like neurogenesis and synaptogenesis, vital for forming new neuronal connections and functional recovery. Persistent inflammation and the presence of neurotoxic substances due to BBB breakdown can impair the viability and functionality of newly generated neural cells (Otero-Ortega et al., 2021). Strategies to enhance brain plasticity, such as rehabilitation and trophic factor administration, are, thus, crucial (Cuartero et al., 2021).

Significance of Promoting the Repair of Disrupted BBB for Patients with Brain Injury

The repair of the disrupted BBB is paramount in the context of brain injuries, given its critical role in maintaining cerebral homeostasis and protecting the neural environment from systemic influences. The integrity of the BBB is integral to the prevention of neuroinflammation and secondary neuronal damage, which are common consequences of brain injuries.

Following brain injury, whether due to stroke, trauma, or neurodegeneration, the compromised BBB becomes a gateway for potentially harmful substances, including immune cells and neurotoxins, to enter the brain. This infiltration exacerbates neuronal damage and can lead to a cascade of detrimental effects, including increased inflammation, oxidative stress, and further degradation of the BBB (Huang et al., 2020; Nian et al., 2020). The disruption of the BBB is not only a consequence of neurological disorders but also a contributing factor to their progression, emphasizing the need for targeted therapeutic interventions focused on BBB repair.

In cerebrovascular diseases such as acute ischemic strokes and intracerebral hemorrhages, as well as in neurodegenerative diseases like AD and PD, BBB dysfunction is increasingly recognized as both a hallmark and a catalyst in the pathogenesis of these conditions (LeVine, 2016; Xiao et al., 2020). The permeability of the BBB allows for the infiltration of immune cells, leading to inflammation and, in cases like multiple sclerosis (MS), subsequent demyelination. This process not only intensifies neuronal damage but also obstructs the brain's intrinsic repair mechanisms, making restoration of BBB integrity crucial.

Moreover, a compromised BBB heightens the risk of intracranial bleeding, especially in the context of therapeutic recanalization, and contributes to the progression of neurodegenerative disorders. It is also being recognized as an early biomarker of neurodegenerative conditions,

signaling the onset of disease before the manifestation of more severe symptoms (Hussain et al., 2021).

The significance of repairing the BBB extends beyond immediate symptom management. It is pivotal in managing the progression of brain injury and predicting patient prognosis. Stabilizing the BBB can mitigate neuronal inflammation, secondary brain damage, and acute neurodegeneration. This highlights the potential of BBB repair as a therapeutic target, offering a strategic point of intervention that could lead to improved patient outcomes and enhanced quality of life. Such measures hold promise not only in mitigating secondary brain damage but also in fundamentally transforming the recovery process for patients with brain injuries.

In summary, promoting the repair of the disrupted BBB is a crucial aspect of treating brain injuries. This approach can potentially reduce the long-term impacts of brain injury, mitigate the progression of neurodegenerative diseases, and improve overall patient outcomes. As research in this area advances, it holds the promise of developing new therapeutic strategies that focus on restoring BBB integrity, underscoring its significance in the realm of neurological disorders and recovery.

Strategies for BBB Protection and Repair Following Brain Injury

Current research on therapeutic strategies

The current therapeutic approaches for protecting and repairing the BBB following brain injury are diverse, encompassing pharmacological treatments, lifestyle modifications, and advanced diagnostic tools. These strategies aim to mitigate BBB disruption, reduce inflammation, and promote recovery of neural function (Table 2).

Advanced imaging methodologies, such as magnetic resonance imaging (MRI), are crucial in evaluating BBB integrity and directing treatment plans. Real-time surveillance of BBB permeability using these technologies facilitates prompt intervention and can considerably impact treatment outcomes (Harris et al., 2023).

Pharmacological interventions are central to BBB protection and repair. Anti-inflammatory drugs (Tułowiecka et al., 2021) and antioxidants (Haghnejad Azar et al., 2017) are routinely employed to counteract the inflammation and oxidative stress that can lead to BBB deterioration. Besides, cyclosporine A (Liu et al., 2022), glucocorticoids (Stokum et al., 2015), minocycline (Strickland et al., 2022), and growth factors (Dordoe et al., 2021) have also shown effectiveness in maintaining BBB integrity and reducing edema.

Minocycline, specifically, is recognized to prevent BBB degradation by inhibiting the activity of MMPs, thus preserving the structural integrity of the BBB (Hayakawa et al., 2008). Acetylsalicylic acid (aspirin) contributes to the protection of the BBB by decreasing its permeability and reducing edema, primarily through the suppression of the NF-κB signaling pathway, which plays a pivotal role in mediating inflammatory responses (Yamamoto et al., 1999). Alpha-tocopherol, also known as vitamin E, further enhances the defense of the BBB with its antioxidant properties, combating oxidative stress and thereby aiding in the maintenance of barrier integrity (Haghnejad Azar et al., 2017). Similarly, lipoxin A4 and its analog, BML-111, exhibit protective effects on the BBB in the context of ischemic stroke. Lipoxins, specifically Lipoxin A4 and its analog BML-111, have shown promise in reducing damage from ischemic stroke by enhancing the integrity of the BBB, reducing the volume of brain damage, and decreasing brain edema. They work by inhibiting the infiltration of

neutrophils and the production of pro-inflammatory cytokines, thereby reducing inflammation. BML-111, in particular, significantly reduces stroke size and protects the cerebral cortex, potentially by decreasing BBB permeability, and has a more potent anti-inflammatory effect than Lipoxin A4 (Tułowiecka et al., 2021).

Recent research has underscored the potential of fibroblast growth factor 20 (FGF20) in defending against BBB disruption following TBI. FGF20 has been demonstrated to upregulate TJ and adhesion junction proteins, reduce cerebral edema, and alleviate functional behavior deficits post-TBI (Chen et al., 2020). It accomplishes this by activating the AKT/GSK3β pathway for cellular protection and suppressing inflammation through the JNK/NFκB signaling pathway. This dual action not only preserves BBB integrity but also tackles the inflammatory response pivotal in secondary injury processes.

Lifestyle modifications, encompassing regular physical activity and dietary changes, are increasingly acknowledged for their role in enhancing BBB function. Aerobic exercises and environmental enhancements have demonstrated potential in animal stroke models for repairing and rejuvenating BBB functionality. These activities are thought to bolster BBB integrity partly by augmenting the expression of endothelial TJ proteins (Wu et al., 2022).

The amalgamation of these approaches constitutes a comprehensive strategy for BBB protection and repair. Pharmacological interventions target the molecular and cellular pathways implicated in BBB disruption, lifestyle modifications fortify overall brain health, and diagnostic tools offer crucial insights into the degree of BBB damage and the efficacy of treatment strategies. Collectively, these approaches represent the current vanguard of therapeutic strategies aimed at mitigating the effects of brain injury on the BBB.

Future research directions

As the field of neurology continues to advance, future research directions in protecting and repairing the BBB following brain injury are poised to explore innovative therapeutic strategies and cutting-edge technologies.

The development of new pharmacological agents is a primary focus of future research. There is a growing interest in exploring drugs that can more effectively target the underlying mechanisms of BBB disruption. This includes investigating medications that can modulate key signaling pathways, such as those involved in inflammation, oxidative stress, and EC function. For instance, research into the role of growth factors like VEGF in BBB repair and regeneration is gaining momentum (Dordoe et al., 2021). In addition, the exploration of the effects of new compounds on BBB integrity, such as the use of RB-222 to neutralize VEGF signaling and reduce brain edema (Zhang et al., 2017), is an area of ongoing investigation.

Another promising area of research is the application of personalized medicine in BBB protection and repair. This approach involves tailoring treatments based on individual differences in BBB structure and function, potentially identified through genomic and proteomic analyses. Personalized treatment strategies could offer more effective and targeted interventions for individuals with brain injuries.

Advancements in diagnostic and monitoring technologies are critical for the future of BBB research. The development of new biomarkers of BBB integrity and the application of artificial intelligence in data analysis could enhance the precision of BBB monitoring. These technologies have the potential to provide deeper insights into BBB function and the

effectiveness of treatments, guiding more effective therapeutic interventions.

Having a deeper knowledge of the long-term effects of brain injury on BBB function remains a crucial area for future research. Longitudinal studies are needed to explore how BBB disruption evolves over time and how it impacts the progression of neurodegenerative diseases and overall brain health. Future research is also likely to focus on integrative and holistic treatment strategies that combine pharmacological, non-pharmacological, and technological approaches. Such strategies would not only target the immediate symptoms but also address long-term brain health and recovery. This comprehensive approach could lead to transformative recovery pathways and improved outcomes for patients with brain injuries.

Conclusion

This review has elucidated the pathophysiology of BBB damage following brain injury, particularly stroke and traumatic brain injury, exploring the cellular and molecular implications and their significance for therapeutic strategies. BBB serves as a vital guardian, maintaining brain homeostasis by collaborating with various cells, such as endothelial cells, and molecules, like TJ proteins, to safeguard the cerebral environment from potential threats. However, brain injury disrupts this equilibrium, leading to the infiltration of neurotoxic substances and inflammatory cells into the brain, thus exacerbating the primary injury and complicating the pathophysiological landscape.

Delving into the impacts of BBB disruption across different phases following brain injury is pivotal in developing novel therapeutic strategies and encompassing pharmacological interventions, to facilitate post-injury recovery. Additionally, safeguarding and restoring BBB

are critical in managing and predicting outcomes for brain injury. With continued advancements, this field harbors the potential to fundamentally reshape the prognosis for patients with stroke and TBI.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions

Ruojing Bai wrote the manuscript, and Xintong Ge reviewed the manuscript.

Funding

This research was supported by grants from the National Natural Science Foundation of China (82071394), Science and Technology Foundation of Tianjin (21JCYBJC01180), and Tianjin Medical University General Hospital Excellent Youth Science Fund (22ZYYYQ03).

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Tables

Table 1 Progression of BBB disruption following brain injury.

Phase	Time Post-Injury	Pathological change	Therapeutic target	Reference
Hyperacute	Within 6 hours	Rapid BBB damage, increased permeability	Immediate medical intervention to mitigate early damage	Bernardo-Castro et al. (2020)
Acute	6 to 60 hours	Intense neuroinflammatory response, increased cytokine activity	Anti-inflammatory interventions	Bernardo-Castro et al. (2020)
Subacute	1 to 3 weeks	Shift towards repair, elevated BBB permeability indicative of repair processes	Therapies promoting repair and mitigating damage	Müller et al. (2021)
Chronic	Beyond 6 weeks	Persistent BBB disruption, inflammation, oxidative stress	Rehabilitation and recovery strategies focusing on BBB repair and neural regeneration	Bernardo-Castro et al. (2020)

Table 2 Current therapeutic approaches for BBB protection.

Strategy type	Specific example	Mechanism of action	Key effect	Reference
Diagnostic tool	MRI	Real-time monitoring of BBB permeability	Enabling timely intervention	Harris et al. (2023)
Pharmacological intervention	Minocycline	Inhibiting the activity of MMPs, preserving the structural integrity of the BBB	Preserving the structural integrity of the BBB	Hayakawa et al. (2008)
	Acetylsalicylic acid (Aspirin)	Decreasing BBB permeability and reducing edema through suppression of the NF-κB signaling pathway	Decreasing BBB permeability and reduces edema	Yamamoto et al. (1999)
	Alpha-tocopherol (Vitamin E)	Combating oxidative stress, aiding in the maintenance of barrier integrity	Enhancing BBB defense through antioxidant properties	Haghnejad Azar et al. (2017)
	Lipoxin A4 and BML-111	Improving BBB integrity by mitigating neutrophil infiltration and reducing pro-inflammatory cytokine and chemokine production; BML-111 also decreases BBB permeability	Reducing stroke size, protects the cerebral cortex, and improves BBB integrity	Tułowiecka et al. (2021)
	Cyclosporine A, Glucocorticoids	Employed for their effectiveness in maintaining BBB integrity and reducing edema	Aids in BBB protection and edema reduction	Stokum et al. (2015), Liu et al. (2022), Strickland et al. (2022)
	Fibroblast Growth Factor 20 (FGF20)	Upregulating tight junction and adhesion junction proteins, activating AKT/GSK3β pathway for cellular protection, and suppressing inflammation through the JNK/NFκB signaling pathway	Reducing cerebral edema and alleviating functional behavior deficits post-TBI	Chen et al. (2020)
Lifestyle modification	Aerobic exercises, dietary adjustments	Increasing endothelial TJ proteins	Improving BBB integrity	Wu et al. (2022)