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Sleep and Blood-Brain Barrier Integrity - Current Understanding and Biological Mechanisms: Literature Review

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Abstract
Background: The blood-brain barrier (BBB) maintains central nervous system homeostasis through the coordinated activity of endothelial cells, pericytes, astrocytes, and other components of the neurovascular unit (NVU). Both sleep and circadian rhythms are critical for preserving BBB integrity.
Aim This review summarizes current understanding of the relationship between sleep and blood-brain barrier function, with particular focus on cellular and molecular mechanisms, and the clinical consequences of sleep disorders.
Material and methods: Articles published between 2010 and 2025 were selected, with earlier publications included when relevant. The search employed the keywords: “blood-brain barrier,” “sleep,” “sleep deprivation,” “sleep loss,” “circadian rhythm,” “glymphatic system,” “oxidative stress,” and “obstructive sleep apnea syndrome.” Sources included PubMed, Google Scholar, and ScienceDirect. Sixty-nine studies were chosen based on relevance, and quality of evidence.

Results: Recent studies demonstrate that optimal sleep architecture plays a regulatory role in the neurovascular unit (NVU). Sleep deprivation and circadian rhythm disturbances have been shown to increase blood-brain barrier (BBB) permeability, induce oxidative stress, impair the glymphatic system, promote persistent low-grade inflammation, and lead to the accumulation of neurotoxic metabolites. Collectively, these changes may accelerate the progression of neurodegenerative diseases.
Conclusion: These findings suggest that maintaining normal sleep patterns and stable circadian rhythms is essential for preserving neurovascular homeostasis and preventing brain degeneration. More translational and clinical research is needed to identify therapeutic targets. Further studies must also clarify the long-term effects of sleep disruption on BBB function and overall brain health.

Keywords:
blood-brain barrier, sleep, sleep deprivation, sleep loss, circadian rhythm, glymphatic system, oxidative stress, obstructive sleep apnea syndrome.

1. Introduction

The blood-brain barrier (BBB) is a crucial protective component of the central nervous system. This highly specialized anatomical and biochemical structure is defined by tight intercellular junctions between endothelial cells, pericytes, astrocytic endfeet, and the extracellular matrix. The BBB regulates the exchange of substances between the blood and nervous tissue, thereby maintaining a stable environment required for neuronal homeostasis. Specific ion channels and transporters mediate this function by preserving the ionic balance necessary for synaptic signaling. Additionally, the BBB restricts the entry of most macromolecules, including albumin, prothrombin, and plasminogen, which are neurotoxic and can induce cellular activation and apoptosis (1).

Disruption of BBB integrity is associated in numerous pathological conditions, including Alzheimer's disease, multiple sclerosis, stroke, Huntington's disease, and neuroinflammatory disorders. Specifically, neurodegenerative diseases often involve BBB dysfunction, characterized by increased permeability, impaired glucose transport, perivascular deposition of blood-derived products, cellular infiltration, and degeneration of pericytes and endothelial cells (2).

The universality of sleep among animal species highlights its fundamental biological significance. Once considered a passive state, sleep is now recognized as an active neurophysiological process vital for maintaining brain health. Recent research has established that sleep plays critical roles in neuronal metabolism, the removal of metabolic waste, and the regulation of intracerebral fluid dynamics. In addition to metabolic regulation and memory consolidation, sleep also modulates glial cell activity and promotes the clearance of neurotoxic substances and metabolic byproducts from the brain’s interstitial space (3).

The identification of the glymphatic system constitutes a major advancement in neurobiology, as it enables cerebrospinal fluid circulation and the removal of metabolic waste products, such as β-amyloid and tau protein. Importantly, glymphatic activity is markedly enhanced during deep sleep, demonstrating a direct role for sleep in brain detoxification and an indirect influence on BBB function (4). Recent evidence suggests that even short periods of sleep deprivation can increase BBB permeability. Furthermore, sleep deprivation disrupts the expression of tight junction proteins, including claudin-5 and occludin, increases oxidative stress, and activates astrocytes and microglia (5).

Although extensive research has been conducted, several critical questions remain unresolved regarding the blood-brain barrier (BBB). Specifically, it is unclear which BBB components are most susceptible to sleep deprivation, how sleep disorders impact human physiology, and whether improving sleep can restore barrier integrity. Sleep disorders, including sleep deprivation and obstructive sleep apnea, are increasingly prevalent in modern society and may represent a significant yet underrecognized risk factor for BBB dysfunction and the development of neurodegenerative diseases.

2. Research materials and methodology

2.1. Data collection and analysis

We included articles published between 2010 and 2025, reviewing earlier publications when necessary for definitions. Only English-language articles with accessible abstracts and relevant keywords were considered. The search employed the following keywords: “blood-brain barrier,” “sleep,” “sleep deprivation,” “sleep loss,” “circadian rhythm,” “glymphatic system,” “oxidative stress,” and “obstructive sleep apnea syndrome.” We focused on studies involving adults aged 19 years and older. Articles were retrieved from PubMed, Google Scholar, and ScienceDirect. From the eligible studies, we selected 69 based on relevance, quality of evidence, and recency, prioritizing high-impact research and recent findings.

2.2. AI

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

3. Results

3.1. Structure and Functions of the Blood-Brain Barrier

The blood-brain barrier (BBB) is a specialized cellular structure that forms a selective interface between the peripheral circulation and the central nervous system (CNS) (5). Recent studies highlight its dynamic properties, demonstrating that the BBB functions as an active regulatory site that precisely controls molecular exchange between the blood and nervous tissue (6). The endothelium's high electrical resistance, low paracellular permeability, and specialized transporters establish the BBB as a critical component in maintaining homeostasis within the brain and spinal cord (5).

3.1.1. Factors Modulating BBB Permeability

The integrity and permeability of the BBB are influenced by a range of internal and external factors. These variations are observed during development, pregnancy, aging, and in response to nutritional status, psychosocial stress, and extreme temperatures. Importantly, as individuals age, the BBB's susceptibility to damage increases, correlating with heightened risk of neurodegeneration and cognitive decline. In addition to these physiological factors, hormones, neurotransmitters, and the functional state of the CNS also modulate barrier properties (7,8). Furthermore, pharmacological and chemical interventions, such as osmotic opening with mannitol or exposure to substances like alcohol, nicotine, cocaine, methamphetamine, or morphine withdrawal, can increase BBB permeability (5,9).

3.1.2. Mechanisms of Molecular Transport Across the Blood-Brain Barrier

Molecular transport across the blood-brain barrier (BBB) occurs through several complementary mechanisms, including both passive and active pathways. Key mechanisms comprise transcellular transport, which involves the movement of molecules through endothelial cells via endocytosis or pores, as exemplified by albumin; facilitated transport mediated by specialized carriers responsible for the uptake of nutrients such as glucose and amino acids; and the diffusion of lipophilic molecules across the plasma membrane, a process regulated by ATP-binding cassette (ABC) transporters (6).

Recent research has identified endocytosis as an important function associated with sleep. Endocytosis across the BBB increases during sleep, and its inhibition leads to an elevated need for sleep (6).

ABC transporters are essential for maintaining BBB integrity by actively removing endogenous metabolites, proteins, and xenobiotics, thereby restricting the entry of peripheral inflammatory mediators into the central nervous system. Additionally, paracellular diffusion through intercellular spaces serves as a complementary mechanism, although it is typically limited by tight junctions under physiological conditions (6). Notably, these transport processes are subject to circadian regulation, as evidenced by the rhythmic oscillations in the diffusion of mediators such as TNFα, leptin, β-amyloid, prostaglandin D_2, and noradrenaline, highlighting the dynamic and complex nature of BBB function (10).

3.1.3. The Neurovascular Unit as the Functional Basis of the BBB

Optimal BBB function relies on coordinated interactions among the various cell types of the neurovascular unit (NVU), including endothelial cells, pericytes, astrocytes, neurons, and microglia. Dysfunction in any of these components can result in increased vascular permeability, immune cell infiltration, and accumulation of toxic metabolites in the interstitial space (11,12,13). BBB dysfunction is strongly linked to the pathogenesis of neurodegenerative diseases such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease (2), and presents significant challenges for drug delivery to the CNS.

3.1.3.1. Endothelial cells

The blood-brain barrier (BBB) is composed of a single layer of specialized endothelial cells that regulate the exchange of substances between the bloodstream and the brain. These endothelial cells are distinct from those found in peripheral tissues. They form tight intercellular junctions between the single monolayer of endothelium, exhibit low rates of transcytosis, and utilize specific transporters to regulate the passage of molecules across their membranes. Additionally, they limit the expression of adhesion molecules, thereby restricting the migration of immune cells into the brain (14,15).

Key tight junction proteins, including occludin, claudin-5, and ZO-1, are regulated by circadian rhythms through the central clock and β-catenin. ABC transporters and TRPM7 ion channels are also subject to rhythmic regulation, thereby affecting circadian modulation of metabolite transport and neurotransmission (6,10,16).

3.1.3.2. Astrocytes

Astrocytes regulate nutrient homeostasis, facilitate neurotransmitter recycling, mediate immune signaling, and provide protection against inflammation. In the suprachiasmatic nucleus (SCN) (17), these functions converge as astrocytes contribute to circadian rhythm synchronization via connexin networks, cyclic ATP release, calcium oscillations, and modulation of GABA signaling. Moreover, deletion of BMAL1 gene disrupts neuronal firing rhythmicity and GABA uptake, underscoring the critical role of astrocytes in maintaining both circadian function and neurotransmitter homeostasis in the brain (10).

3.1.3.3. Pericytes

Pericytes reside within the basement membrane of cerebral microvessels, and their density is inversely correlated with BBB permeability (11). They regulate blood flow, facilitate the removal of toxic metabolites, modulate endothelial gene expression, and ensure appropriate polarization of astrocyte endfeet (12). Recent findings indicate that BMAL1 gene deletion in pericytes causes an age-dependent reduction in vascular coverage and increased BBB permeability. This effect is linked to decreased platelet-derived growth factor receptor beta (PDGFRβ) expression, which is essential for pericyte recruitment and function (10).

3.1.3.4. Microglia

Microglia are phagocytic cells within the central nervous system (CNS) that rapidly respond to neuroinflammation and tissue damage by increasing phagocytic activity and cytokine production (18). Disruption of microglia leads to significant physiological consequences. For instance, microglial ablation in mice disrupts the diurnal rhythms of various physiological processes and alters circadian clock gene and protein expression in both the suprachiasmatic nucleus (SCN) and the hippocampus. Circadian rhythms also tightly regulate microglial inflammatory responses; upon immune activation, microglia produce increased levels of pro-inflammatory cytokines, particularly during the light phase. Moreover, microglial responses to glucocorticoids in stress-induced neuroinflammation display circadian dependence, which underlies their diurnal rhythmicity in response to inflammatory stimuli (10,19).

3.2. Sleep and the Circadian Rhythm

3.2.1. Characteristics and Importance of Sleep

Sleep is a complex and active neurophysiological process essential for maintaining homeostasis in both the brain and the entire body. It is defined by unconsciousness, reduced motor activity, and decreased alertness (20). According to the World Health Organization (2004), "sleep is a basic human need and is essential for good health, good quality of life, and optimal daytime performance." Numerous metabolic, immunological, and reparative processes occur during sleep, which are critical for overall health and physiological functioning (21).

The evolutionary persistence of sleep across the lifespan remains incompletely understood. Experimental evidence demonstrates that sleep serves regenerative functions, including the removal of neurotoxic metabolic waste products that accumulate during wakefulness (22,23). The duration, quantity, and quality of sleep vary according to age and sex. The sleep-wake cycle regulates the release of hormones, neurotransmitters, and cytokines, which are essential for maintaining optimal organ and system function (21).

3.2.2. Sleep Architecture and Mechanisms

Sleep is composed of two primary phases: rapid eye movement (REM) sleep and non-rapid eye movement (NREM), which alternate in a cyclical pattern throughout the sleep period. REM sleep is marked by intense brain activity and vivid dreaming, characterized by low-voltage, fast EEG activity and near-complete muscle atonia (24). NREM sleep consists of four stages (NREM 1-4), with synchronous slow-wave EEG activity (SWA) being the most distinctive feature. SWA, which predominates during deep sleep, serves a critical homeostatic function: it increases after sleep deprivation and decreases following naps. The mechanisms underlying the generation of slow-wave activity (SWA) are not fully understood, but evidence suggests that SWA is crucial for brain regenerative processes, including the clearance of the perivascular space (25,26,27,28).

Research has demonstrated that sleep enhances perivascular clearance. Therefore, sleep may play a restorative role in neurodegenerative diseases by promoting this mechanism (6). Clinical studies in both humans and animals have confirmed that sleep deprivation results in the accumulation of amyloid-beta and tau aggregates (29,30). Recent studies have demonstrated a direct association between sleep-related neuronal activity and both cerebrospinal fluid (CSF) and blood flow. Specifically, slow-wave sleep is associated with increased CSF flow amplitude relative to the awake state, and an inverse relationship between CSF and blood flow has been observed. However, in vivo studies have not yet established whether sleep or sleep deprivation directly affects the rate of molecular clearance from the human brain (23).

3.2.3. Mechanisms of Sleep Regulation

Sleep is governed by two primary interacting mechanisms:

The homeostatic process represents the biological requirement for sleep, which intensifies with prolonged wakefulness and diminishes during sleep. Adenosine serves as a primary neurochemical mediator in this process by accumulating in subcortical brain regions and inhibiting excitatory neuronal activity, thereby facilitating sleep onset (31).

The circadian process (circadian rhythm) synchronizes the sleep-wake rhythm with the light-dark cycle. It is responsible for regulating melatonin secretion, body temperature, and the neural activity of systems that promote sleep onset and wake (6,32).
The interaction between these two processes is essential for maintaining normal sleep architecture and supporting optimal brain restoration.

3.2.4. Circadian Rhythm

The circadian rhythm is an endogenous, approximately 24-hour cycle regulated by the molecular biological clock. While it can be synchronized by external cues such as light, temperature, or food intake, it operates independently of these factors (6). The central circadian clock is located in the suprachiasmatic nucleus (SCN) of the hypothalamus, which coordinates the activity of peripheral clocks throughout the body (32).
The SCN coordinates peripheral clocks through neural mechanisms involving the sympathetic and parasympathetic pathways, as well as humoral mechanisms. These humoral mechanisms include neuropeptide release and activation of the hypothalamic-pituitary-adrenal axis, which regulates melatonin secretion from the pineal gland and the release of glucocorticoids and catecholamines from the adrenal cortex (10,33).
This rhythm also regulates the activity of the permeability-glycoprotein multidrug transporter, which actively expels both endogenous and exogenous molecules from the central nervous system. The activity of this transporter decreases at night, leading to increased permeability of various substrates into the brain during this period (6).
SCN neurons, primarily GABAergic, control the differential expression of neuropeptides: in the nuclear region, vasoactive intestinal peptide (VIP), calretinin, and gastrin-like peptide predominate, while in the cortical region, arginine vasopressin (AVP), angiotensin II, prokineticin-2, and met-enkephalin are more prominent (10). The SCN is unique among mammalian brain regions for its strong cellular coupling, which enables autonomous oscillations in neuronal activity and circadian gene expression (34,35). Peripheral clocks regulate the rhythmicity of body temperature, metabolism, and hormone secretion by integrating signals from the central circadian clock (36).

3.2.5. Consequences of Circadian Rhythm Disturbances

Disruptions of the circadian rhythm constitute a significant public health problem. They result from factors such as shift work, frequent time zone changes, sleep disorders, and excessive exposure to blue light from electronic devices. The effects of dysregulation of the circadian rhythm include an increased risk of: neurological and neurodegenerative diseases, metabolic disorders (obesity, insulin resistance), mood and cognitive disorders, cancer, intestinal barrier dysfunction, and changes in the gut microbiota (10,37).

3.3. Blood-brain barrier impairment induced by sleep loss

Sleep is essential for maintaining central nervous system homeostasis, as evidenced by the wide range of physiological consequences resulting from sleep deprivation. Studies in both animal models and humans demonstrate that sleep deprivation leads to cognitive impairment, metabolic alterations, cardiovascular and immune dysfunction, impaired neurogenesis, and blood-brain barrier (BBB) dysfunction (38).

Among these effects, the influence of sleep deprivation on BBB integrity and function, a critical component of neuroprotection, is especially significant.

Normal sleep maintains the functional stability of the neurovascular unit (NVU), which comprises endothelial cells, pericytes, and astrocytes. These components regulate cerebral vascular permeability, mediate the transport of substances, and protect against proinflammatory and toxic factors. Both acute and chronic sleep deprivation increase BBB permeability, disrupt molecular transport, and heighten brain vulnerability to metabolic and inflammatory damage (38).

Acute sleep deprivation, defined as less than 48 hours, results in significant cognitive deficits such as impaired memory, learning, and emotional regulation (39). Concurrently, microglial activation and increased astrocytic phagocytosis of synaptic structures occur, which, if persistent, may contribute to neuronal degradation (40). Sleep deprivation also induces sterile inflammation, attributed to increased BBB permeability and enhanced entry of proinflammatory mediators from the peripheral circulation (5,41,42). Extended deprivation can result in hallucinations, severe cognitive impairment, and, in animal models (such as rats and flies), death (43,44,45).

Chronic sleep restriction increases BBB permeability by activating adenosine signaling, particularly through the A2A receptor in the hippocampus. However, brief periods of sleep, such as 40 or 120 minutes, restore BBB integrity. Furthermore, regional differences in vulnerability may arise from differential regulation of adenosine receptors and additional mechanisms, including pinocytosis and local inflammation (46). In addition, studies in flies and rodents demonstrate circadian modulation of brain clearance: during wakefulness, P-glycoprotein (Pgp)-dependent active outflow predominates, whereas endocytosis and perivascular flow are enhanced during sleep. Notably, sleep disturbances can disrupt this balance, in part by increasing cytokine levels that further elevate BBB permeability (6).

Other studies demonstrate that sleep deprivation significantly increases CD44 expression in the hippocampus. Building on this, CD44 overexpression in astrocytes impairs blood-brain barrier integrity by altering tight junction proteins and promoting NANOG gene expression (47).

Recent research has highlighted the role of sleep in facilitating the removal of metabolic waste products from the brain. During sleep, interstitial fluid (ISF) volume increases by up to 60 percent, and aquaporin-4 (AQP4) water channels in astrocytic end feet enhance metabolite transport and clearance. This mechanism supports the elimination of neurotoxic proteins, such as β-amyloid (48). Additionally, during NREM sleep, low-frequency neuronal oscillations promote memory consolidation and regulate brain metabolic activity, accompanied by coordinated changes in electrophysiology, hemodynamics, and cerebrospinal fluid flow (49).

Chronic sleep deprivation is a significant risk factor for Alzheimer's disease and other neurodegenerative disorders (49). While sleep disturbances in dementia frequently arise from damage to circadian neurons in the suprachiasmatic nucleus, increasing evidence suggests that sleep deprivation independently accelerates the accumulation of abnormal proteins. Impaired clearance of β-amyloid and tau proteins (22,23), due to dysfunction of the glymphatic system and BBB disruption, may represent a central mechanism of neurotoxicity.

Postmortem and experimental studies indicate that BBB breakdown facilitates seizure activity. Epilepsy exhibits a distinct cyclicity of seizures, which varies according to the time of day and the specific brain lobe involved. Dysregulation of the molecular clock and sleep deprivation both reduce the seizure threshold, partly through inflammatory pathways and alterations in neuronal excitability. While the precise relationship between BBB circadian rhythms and seizures remains to be fully elucidated, current evidence indicates that sleep and circadian rhythm disturbances play a significant role in the pathophysiology of epilepsy (6).

In older adults, sleep fragmentation, which is prevalent in aging and neurodegenerative diseases, further exacerbates BBB dysfunction. Also perivascular clearance is reduced in the aging brain (6). This condition facilitates the entry of inflammatory mediators and disrupts brain molecular homeostasis. Persistent sleep fragmentation may contribute to the progression of neurodegenerative pathology (7).

In vivo imaging studies demonstrate that a single night of complete sleep deprivation reduces the clearance of markers such as gadobutrol from the brain. Notably, diminished elimination persists even after a subsequent night of sleep. These alterations are observed in the cerebral cortex, white matter, and limbic structures. As gadobutrol may indicate the transport of hydrophilic metabolites through extravascular pathways, these findings suggest that even brief sleep disruptions can impair the elimination of neurotoxic compounds (23).

Chronic sleep deprivation decreases the expression of tight junction proteins, such as claudin-5 and occludin, thereby increasing barrier permeability. It also promotes activation of inflammatory cells, oxidative stress, enhances endothelial transcytosis, and stimulates the release of proinflammatory cytokines (5,38).

3.3.1. Glymphatic system

The brain's high metabolic demands, combined with the restrictive properties of the blood-brain barrier (BBB), create unique challenges for waste clearance. Unlike peripheral tissues, which rely on plasma ultrafiltrate and lymphatic vessels for fluid transport and detoxification, the brain lacks a conventional lymphatic system. Therefore, a specialized mechanism is necessary for waste removal. The glymphatic system, a recently identified pathway, performs this role by facilitating the clearance of metabolites from the central nervous system (50).

The glymphatic system functions through perivascular channels created by the terminal processes of astrocytes, which line the spaces around blood vessels. These channels allow cerebrospinal fluid (CSF) to enter brain tissue and mix with interstitial fluid. This process generates convective flow, facilitating the removal of soluble proteins, toxins, and metabolites. In addition to waste clearance, the glymphatic system distributes essential compounds, including glucose, lipids, amino acids, growth factors, and neuromodulators, throughout the brain (51).

Glymphatic system activity is strongly modulated by the sleep-wake cycle. Research demonstrates that glymphatic flow increases by up to 60% during sleep compared to wakefulness. Peak activity occurs during slow-wave (NREM) sleep, when reduced neuronal activity and metabolism promote the expansion of intercellular spaces and enhance cerebrospinal fluid transport. During NREM sleep, the glymphatic system actively removes neurotoxic metabolites, including β-amyloid, which accumulate in the brain during wakefulness. This clearance is critical for preventing the deposition of these substances and for protecting neurons from oxidative stress and synaptic dysfunction (3,52).

3.3.2. Dysregulation of Tight Junction Proteins

Endothelial cells that form the blood-brain barrier (BBB) are connected by specialized protein structures known as tight junctions (TJs). The principal components of these junctions are claudin-5, occludin, and the cytoplasmic proteins ZO-1 and ZO-2, which stabilize the complexes that maintain cellular adhesion and barrier integrity (53).

Chronic sleep restriction (CSR) results in persistently reduced sleep efficiency and a decreased proportion of NREM and REM sleep, driven by increased sleep fragmentation and prolonged wakefulness (5). Evidence indicates that even short-term sleep deprivation reduces the mRNA and protein levels of claudin-5 and occludin, and alters the localization of ZO-1 from the cell periphery to the cytoplasm. These structural modifications compromise intercellular junction integrity and increase BBB permeability (5).

3.3.3. Oxidative stress

Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) production and antioxidant system activity, is a major factor influencing blood-brain barrier (BBB) function. The cerebral vasculature is particularly vulnerable to ROS-induced damage, as processes such as excitotoxicity, mitochondrial dysfunction, impaired iron metabolism, and programmed cell death (pyroptosis and necroptosis) elevate ROS levels and contribute to endothelial dysfunction. ROS destabilize tight junction proteins, activate matrix metalloproteinases (MMPs), impair transporter function, and trigger local inflammatory responses (54).

Sleep is essential for reducing oxidative stress by facilitating the removal of reactive molecules that accumulate during wakefulness. Both ROS and reactive nitrogen species (RNS) serve as signaling molecules that regulate redox processes and influence sleep homeostasis. The transcription factor NRF2 maintains redox balance, and its dysfunction is linked to sleep disorders. Consequently, targeting the NRF2 pathway may represent a potential therapeutic strategy (55).

In animal models, extreme sleep deprivation induces severe inflammation, increases mortality, and elevates prostaglandin D_2 (PGD_2) levels, with enhanced transport across the blood-brain barrier. Inhibition of the PGD_2/DP1 axis alleviates these adverse outcomes, supporting the association between sleep, oxidative stress, and immune responses (56).

CSR also affects endothelial nitric oxide synthase (eNOS), inducible nitric oxide synthase (iNOS), endothelin-1, and glucose transporters in cerebral microvessels. These disturbances include both reduced expression of glucose transporters at the BBB level and reduced GLUT1 function in the brain itself (5). In animal models, chronic sleep restriction leads to decreased levels of eNOS and iNOS, suggesting reduced nitric oxide production - an important mediator of blood flow and maintenance of BBB homeostasis (57,58).

Furthermore, oxidative stress can directly disrupt tight junctions, by promoting occludin relocalization (59).

Another cause of endothelial dysfunction in chronic sleep restriction (CSR) is increased COX-2 activity. Unlike nitric oxide, which promotes vasodilation and reduces oxidative stress, COX-2 is associated with impaired vascular reactivity and ROS generation, which exacerbates endothelial damage. Elevated COX-2 levels, coupled with decreased iNOS and eNOS expression, observed in CSR reflect increased proinflammatory processes and vascular dysfunction (5).

Despite the extensive structural and functional alterations induced by chronic sleep restriction, evidence indicates that these dysfunctions may be reversible. Studies have demonstrated that BBB impairment that develops after 6 days of CSR can resolve after 24 hours of recovery sleep. These findings suggest that reparative processes during sleep are essential for preserving neurovascular integrity and mitigating the long-term effects of sleep deprivation (5).

3.3.4. Inflammation

Chronic sleep loss is associated with elevated levels of inflammatory mediators, which, as shown in studies, compromise the integrity of the blood-brain barrier (BBB) and contribute to its disruption (38).

Experimental studies have demonstrated that both acute and chronic sleep loss impair immune responses, as evidenced by reductions in the number and function of immune cells, as well as elevated levels of proinflammatory mediators, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, IL-17A, interferon-γ (IFNγ), and C-reactive protein (CRP) (6). These mediators influence the expression of tight junction proteins. Beyond immune-derived inflammatory mediators, sleep loss also increases levels of other inflammatory molecules, including cyclooxygenase-2 (COX-2) (5), nitric oxide synthase (NOS), endothelin-1 (ET-1), vascular endothelial growth factor (VEGF), intercellular adhesion molecule-1 (ICAM), and insulin-like growth factor-1 (IGF-1).

Interleukin-1β (IL-1β) released from activated microglia increases blood-brain barrier (BBB) permeability, likely by inhibiting astrocyte-derived signals that support barrier integrity (60). These observations suggest that IL-1β disrupts communication between astrocytes and endothelial cells, impairing their coordinated role in maintaining the BBB (61).

Sleep deprivation increases **tumor necrosis factor-α (TNF-α)** and **interleukin-6 (IL-6)** expression, which, in turn, reduces tight junction protein expression, including ZO-1, occludin, claudin-1, and claudin-5. This reduction forms gaps between endothelial cells, as demonstrated in studies with rats and mice (6). TNF-α and IL-6 exert region-specific effects on the BBB, partly due to variations in receptor expression across different brain regions. The precise role of IL-6 in sleep regulation remains unclear. Although IL-6 levels change following sleep deprivation, its direct effect on barrier integrity remains poorly established. IL-6 may primarily modulate other proinflammatory cytokines rather than directly affecting tight junction proteins (38). Sustained, moderate elevations in TNF-α during sleep deprivation may contribute to BBB dysfunction. Specifically, these elevations can overactivate microglia and astrocytes (38) and stimulate the NFκB signalling pathway, which, in turn, increases prostaglandin E levels through COX-2 (38).

Interleukin-17A (IL-17A), a cytokine associated with Th17 cells and elevated in several autoimmune diseases, increases epithelial and endothelial permeability by destabilizing tight junctions. In vitro studies confirm that higher concentrations of IL-17A increase endothelial cell permeability (38). Additionally, **C-reactive protein (CRP),** a major acute-phase protein, disrupts the blood-brain barrier. This disruption elevates oxidative stress, leading to the oxidation of tight junction proteins and representing a significant risk factor for vascular dysfunction in the central nervous system (38).

Additionally, chronic sleep deprivation disrupts pericyte-endothelial cell interactions by reducing the expression of PDGFR-β and connexin-43. This results in pericyte detachment from the vessel, reduced levels of claudin-5 and occludin, and increased BBB permeability to exogenous molecules. Simultaneously, activation of proinflammatory signaling pathways is observed, including, among others. NFκB, MMP-9, and adenosine A2A receptors. These results highlight the significant role of pericytes in maintaining BBB integrity and their sensitivity to sleep disturbances (62).

In summary, sleep loss impairs blood-brain barrier permeability through several concurrent mechanisms, including dysfunction of the glymphatic system, dysregulation of tight junction proteins, oxidative stress, and increased inflammation. Nevertheless, additional, unidentified mechanisms may exist. Further research is required to fully elucidate how sleep loss affects blood-brain barrier integrity.

3.4. Obstructive Sleep Apnea Syndrome (OSAS)

Obstructive sleep apnea syndrome (OSAS) is a prevalent yet frequently underdiagnosed disorder among older adults, with incidence increasing significantly after the age of 60. OSAS elevates the risk of cardiovascular and cerebrovascular diseases, as well as cognitive impairment (63), all of which have substantial clinical implications for diagnosis and management in geriatric care. Diagnosis of OSAS, defined by an apnea-hypopnea index (AHI) greater than 5 events per hour, is primarily managed with continuous positive airway pressure (CPAP) therapy. A major challenge in clinical practice is identifying individuals most at risk of cognitive decline to enable timely intervention and optimize patient outcomes. Emerging evidence implicates disruption of the blood-brain barrier (BBB) as a central mechanism linking OSAS to central nervous system (CNS) dysfunction.

Intermittent hypoxia, sleep fragmentation (64), and circadian rhythm disturbances characteristic of OSAS collectively increase BBB permeability, facilitating the entry of neurotoxic substances into the brain parenchyma (6). Intermittent hypoxia promotes cytokine release and upregulates beta- and gamma-secretase activity, thereby increasing amyloid β (Aβ) production (65). Simultaneously, sleep fragmentation impairs glymphatic clearance of Aβ and tau, disrupts tight junction integrity, and exacerbates neuroinflammation and neurodegeneration.

Exosomes, which are endosome-derived extracellular vesicles, are elevated in the plasma of patients with OSAS and play a critical role in mediating these pathogenic processes. These vesicles can cross the BBB and transport neurotoxic proteins, including Aβ and tau, thereby serving as accessible, minimally invasive biomarkers of neurodegenerative changes (66).

In vitro studies demonstrate that exosomes isolated from OSAS patients increase BBB permeability and decrease the expression of essential tight junction proteins, such as ZO-1 and claudin-5, while maintaining occludin levels (67,68). These changes in brain endothelium compromise BBB integrity and allow serum components to enter the CNS, resulting in synaptic dysfunction, microglial activation, and neurotoxic alterations implicated in the pathogenesis of vascular dementia and Alzheimer's disease. Impaired glymphatic function and persistent oxidative stress further impede the clearance of these proteins, reinforcing the mechanistic association between OSAS and neurodegeneration (66).

Overall, current evidence indicates that severe OSAS in older adults is closely associated with BBB dysfunction. Exosomes function as both biomarkers and mediators of these changes, supporting the development of novel diagnostic and therapeutic strategies. Nevertheless, several limitations remain, and further research is needed (66,69).

3.5. Further Directions for Research

Substantial evidence demonstrates a relationship between sleep and the integrity of the blood-brain barrier (BBB), although the underlying mechanisms remain incompletely understood. Longitudinal studies are required to clarify the effects of both acute and chronic sleep deprivation on BBB function. Further research should also evaluate whether interventions that improve sleep quality, such as positive airway pressure therapy for obstructive sleep apnea syndrome (OSAS), light therapy or melatonin for circadian rhythm regulation, and strategies to enhance glymphatic flow, including optimizing sleep posture or promoting slow-wave sleep, can reverse or mitigate BBB damage. These interventions may reduce the risk of developing long-term neurodegenerative disorders.

4. Discussion

Evidence increasingly shows a strong link between sleep and blood-brain barrier (BBB) integrity. Non-rapid eye movement (NREM) sleep supports the glymphatic system, which efficiently clears neurotoxic metabolites such as β-amyloid and tau protein. Acute or chronic sleep deprivation disrupts tight junction protein regulation, raises oxidative stress, and increases microglial and astrocyte activation. These changes elevate BBB permeability and the risk of neuroinflammatory and neurodegenerative processes.

These findings indicate that sleep protects central nervous system health, while sleep deprivation may accelerate pathological processes seen in neurodegenerative diseases such as Alzheimer's disease. Additionally, sleep disorders like obstructive sleep apnea syndrome, which involve sleep fragmentation and intermittent hypoxia, further worsen BBB dysfunction and promote the entry of proinflammatory cytokines and neurotoxic proteins into the brain.

Despite extensive research, significant knowledge gaps remain. These include the regional vulnerability of the BBB to sleep deprivation, the effects of different sleep stages on cerebrospinal fluid dynamics, the molecular mechanisms of cell interactions within the neurovascular unit, and strategies to protect the BBB during chronic sleep deprivation. Further research in these areas may improve understanding of neurophysiological processes and support the development of new therapies and preventive measures.

5. Conclusions

Sleep is essential for brain homeostasis and preserves the integrity of the blood-brain barrier (BBB). Circadian rhythms are regulated by the central biological clock in the suprachiasmatic nucleus (SCN). They influence the activity of cells that make up the neurovascular unit (NVU) of the BBB. These cells are critical for maintaining the barrier's structure and function, as well as for optimal nervous system function. Disruptions in circadian rhythms, due to environmental or pathological factors, can disturb clock-related molecular pathways. This may contribute to chronic neurodegenerative and systemic diseases.

Recent studies show that proper sleep architecture is vital for BBB integrity and brain homeostasis. Chronic sleep deprivation and disturbances in circadian rhythms occur in conditions like obstructive sleep apnea. These problems increase BBB permeability, activate glial cells, and disrupt tight junctions between endothelial cells. They also induce oxidative stress, impair glymphatic function, and trigger low-grade inflammation. These changes let neurotoxic metabolites accumulate and may speed the progression of neurodegenerative diseases, including Alzheimer's and Parkinson's disease.

The literature suggests that interventions focused on enhancing sleep quality, modulating circadian rhythms, and utilizing pharmacological strategies to support BBB regeneration and protection may substantially mitigate the long-term consequences of sleep deprivation. These interventions can help maintain BBB integrity, limit neurotoxic metabolite accumulation, and reduce inflammatory responses, thereby reducing the risk or progression of neurodegenerative diseases. Nevertheless, additional translational and clinical research is required to identify specific therapeutic targets and to delineate the long-term effects of sleep disorders on brain function and the development of neurodegenerative diseases.

In summary, sleep is a key mechanism for neurovascular integrity. It protects the brain from chronic metabolic and inflammatory disorders. Understanding how sleep influences blood-brain barrier function could open new opportunities for the prevention and treatment of neurodegenerative diseases.

6. Disclosure

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