J Current Biomed Report
ISSN: 2717-1906
2025, Volume 6, Number 2
Review Paper

Molecular mechanism linking sleep disturbances to neurodegenaration

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ABSTRACT

Article info:
Received: 20 May 2025
Accepted: 17 Jun 2025

Keywords:
Sleep disturbances
Neurodegeneration
Neuroinflammation
Circadian rhythm
Oxidative stress

Sleep disturbances are increasingly recognized as both early indicators and potential contributors to the progression of neurodegenerative diseases. Disrupted sleep compromises glymphatic clearance and synaptic homeostasis, promoting the accumulation of neurotoxic proteins such as amyloid-β, tau, and α-synuclein. Concurrently, irregular sleep patterns and circadian rhythm disturbances activate neuroinflammatory pathways, including microglial activation, NF-κB signaling, and the NLR family pyrin domain containing 3 (NLRP3) inflammasome**,** thereby accelerating neuronal damage. Additional mechanisms, such as mitochondrial dysfunction, oxidative stress, and imbalances in neurotransmitter systems including orexin and melatonin, further reinforce the bidirectional relationship between sleep impairment and neurodegeneration. Despite these insights, critical gaps remain, particularly the absence of reliable biomarkers for simultaneously assessing sleep quality, neuroinflammation, and disease progression, as well as limited research on disorders beyond Alzheimer's and Parkinson's disease. Therapeutic strategies show promise, ranging from pharmacological interventions targeting inflammatory pathways to non-pharmacological approaches such as chronotherapy, light therapy, and cognitive behavioral therapy for insomnia. Emerging modalities, including RNA-based therapies targeting pathogenic proteins and artificial intelligence (AI) for early detection and personalized treatment of sleep abnormalities, offer novel opportunities for intervention. This narrative review explores the molecular mechanisms underlying sleep disturbances in neurodegenerative diseases, identifies critical gaps in current research, and discusses emerging therapeutic strategies aimed at mitigating sleep-related neurodegeneration.

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1. Introduction

Sleep is a fundamental physiological need and plays an essential role in brain health and cognitive function. Adequate nighttime sleep allows neurons to rest, consolidates memory, facilitates the clearance of metabolic waste, and maintains synaptic stability [1]. Understanding the relationship between sleep quality and pathological mechanisms in the brain has become a central focus in modern neuroscience. Sleep disruption can trigger a cascade of cognitive and neurobiological consequences that contribute to the onset and progression of neurodegenerative diseases [2]. Recent epidemiological studies have shown that sleep disturbances such as insomnia, rapid eye movement (REM) sleep behavior disorder, and sleep apnea are common among patients with neurological disorders including Alzheimer's disease, Parkinson's disease, multiple sclerosis, and epilepsy. More than 60% of individuals with Alzheimer's experience some degree of sleep disturbance, which may appear years before the onset of cognitive symptoms [3]. In recent years, research on sleep disturbances has shifted from purely clinical observations to exploring the molecular mechanisms underlying neurological diseases. Evidence indicates that insufficient sleep increases oxidative stress, impairs interstitial brain clearance particularly glymphatic system function activates inflammatory pathways, and alters the expression of circadian rhythm regulated genes. These molecular changes promote the accumulation of β-amyloid and α-synuclein, which play central roles in the development of many neurodegenerative disorders [4]. Figure 1 shows the pathological pathway from sleep disorders to neurodegeneration. Sleep disturbances can also affect organs outside the brain, such as the lungs, increasing susceptibility to lung cancer. Insufficient sleep alters the expression of over 3,000 genes in lung tissue, creating a favorable environment for viral infections and disrupting tissue homeostasis. Additionally, increased pro-inflammatory cytokines and decreased antioxidant systems promote apoptotic cell death and structural damage to the alveoli [5]. The aim of this study is to examine the relationship between sleep disturbances and neurodegeneration, with a focus on the molecular mechanisms involved. Particular attention will be given to glymphatic dysfunction, oxidative stress, neuroinflammation, and the role of circadian rhythm disruption in regulating neuronal gene expression. Investigating these pathways may aid in the early diagnosis of neurodegenerative diseases and contribute to the development of targeted therapeutic interventions aimed at improving sleep and slowing disease progression. In conclusion, sleep disturbances should not be regarded merely as secondary symptoms of neurodegenerative disorders, but rather as active contributors to disease onset and progression. A deeper understanding of the interplay between sleep disturbances and their associated molecular mechanisms will open new therapeutic opportunities to combat cognitive decline and promote brain health in aging populations.

2. Effects of oxidative stress

Oxidative stress occurs when the equilibrium between the production of reactive oxygen species (ROS) and the cell's antioxidant defenses is disturbed. As a key driver of neuronal injury, it significantly contributes to the development and progression of neurodegenerative disorders. The brain is especially susceptible due to its high oxygen demand, abundance of polyunsaturated fatty acids, and comparatively low antioxidant capacity [6]. Sleep disturbances, including inadequate duration and poor sleep quality, further increase ROS levels while diminishing the activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) [7].

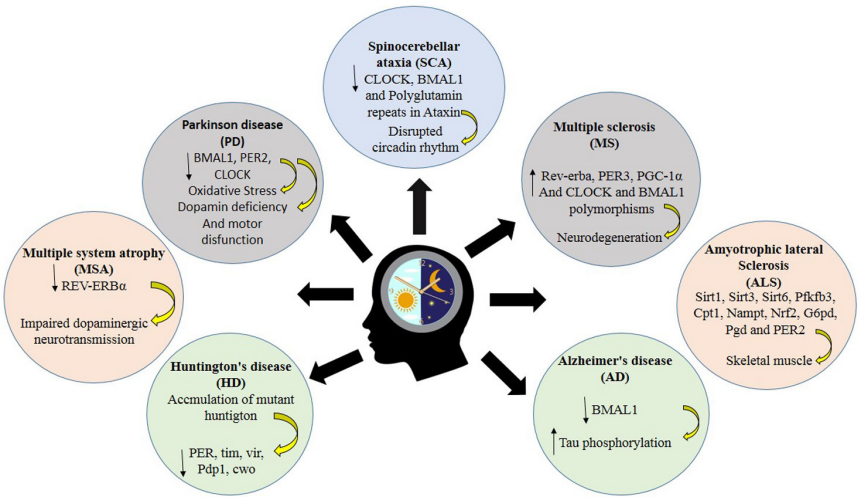

Figure 1. Pathological pathway from sleep disorders to neuronal degeneration: Insomnia and other sleep disorders increase oxidative stress (ROS) and activate inflammatory pathways, leading to the secretion of pro-inflammatory cytokines such as TNF and IL-6, which ultimately causes neuronal damage and degeneration.

In addition, insufficient sleep triggers inflammatory signaling pathways, particularly NF-κB, which amplifies free radical production and promotes the release of pro-inflammatory cytokines. This interplay between oxidative stress and inflammation leads to DNA damage, lipid peroxidation, and mitochondrial dysfunction, ultimately resulting in neuronal loss. Elevated ROS levels also accelerate the aggregation of pathological proteins; for instance, they promote abnormal Tau phosphorylation in Alzheimer's disease and impair α-synuclein clearance in Parkinson's disease [8,9].

Mitochondrial electron leakage during sleep deprivation exacerbates ROS formation, and given the limited regenerative ability of neurons, these effects are often cumulative and irreversible. Consequently, interventions aimed at mitigating oxidative stress represent a promising avenue to prevent or slow neurodegenerative progression [10].

3. Neuroinflammation induced by sleep disturbances

Neuroinflammation is both a consequence and a driver of neuronal dysfunction. Sleep disturbances particularly insufficient or fragmented sleep are potent triggers of inflammatory responses within the central nervous system (CNS). Sleep plays a crucial role in modulating the balance of immune activity in the CNS, and its disruption alters cytokine expression, promotes chronic microglial activation, and sustains the release of pro-inflammatory mediators. This persistent inflammatory milieu initiates a cascade of cytotoxic events, damaging neuronal and glial cells and disrupting synaptic integrity. Over time, the resulting neuroinflammatory state contributes to disease progression in conditions such as Alzheimer's, Parkinson's, and other neurodegenerative disorders [11,12].

3.1 Role of cytokines

Cytokines act as central mediators of neuroinflammation and play a pivotal role in linking sleep disturbances to neuronal dysfunction. Pro-inflammatory are markedly elevated following sleep loss, promoting oxidative stress, mitochondrial impairment, and synaptic dysfunction. Imbalances in this cytokine network contribute to sustained microglial activation and progressive neurodegeneration, highlighting the importance of targeting cytokine signaling pathways in therapeutic interventions [2,13].

3.1.1 TNF-α

Tumor necrosis factor-alpha (TNF-α) functions as a pivotal pro-inflammatory cytokine within the central nervous system, critically modulating immune responses. TNF-α mediates its effects by engaging tumor necrosis factor receptor 1 (TNFR1) and TNFR2 receptors, thereby initiating downstream signaling through the NF-κB and mitogen-activated protein kinase (MAPK) pathways. Activation of these cascades leads to upregulation of inflammatory gene expression and, particularly under oxidative stress conditions, can precipitate programmed neuronal cell death. The interplay between TNF-α signaling and cellular oxidative stress underscores its central role in neuroinflammation and neurodegenerative processes [13].

3.1.2 IL-6

Interleukin-6 (IL-6) is a pleiotropic cytokine capable of inducing a systemic inflammatory response, activating microglia and astrocytes in the CNS, and crossing the blood-brain barrier to regulate or exacerbate neuroinflammation [14]. Both TNF-α and IL-6 are significantly elevated in response to sleep disturbances, leading to increased ROS production and impaired mitochondrial function. In both human and animal studies, elevated levels of these cytokines animal studies, elevated levels of these cytokines accelerate β-amyloid deposition and promote Tau phosphorylation two hallmarks of Alzheimer's disease. Chronic elevation also alters neurotransmitter balance, particularly glutamate and gamma-aminobutyric acid (GABA), thereby disrupting excitatory inhibitory homeostasis and impairing cognitive and memory function [15].

3.1.3 IL-1β

Interleukin-1 beta (IL-1β) is a major pro-inflammatory cytokine secreted by activated microglia in response to neuronal stress or injury. IL-1β directly activates the NLR family pyrin domain containing 3 (NLRP3) inflammasome complex, increases blood-brain barrier permeability, and stimulates the production of other cytokines. In sleep disturbances, IL-1β levels are elevated in both cerebrospinal fluid (CSF) and brain tissue, and are associated with disruption of REM and slow-wave sleep cycles. IL-1β contributes to neuroinflammation and accelerates cognitive decline in neurodegenerative disorders [16].

3.1.4 IL-10

Interleukin-10 (IL-10) is a potent anti-inflammatory cytokine produced primarily by astrocytes and microglia. It suppresses the production of IL-6, TNF-α, and IL-1β, and inhibits NF-κB activation, thereby reducing neuroinflammation and protecting neurons. Chronic sleep disturbances are associated with reduced IL-10 levels, which in turn exacerbate inflammation and neurodegeneration. Experimental upregulation of IL-10 in animal models has been shown to reduce amyloid deposition and improve cognitive outcomes [17].

3.1.5 IFN-γ

Interferon-gamma (IFN-γ), derived from T cells and microglia, plays a role in antiviral defense and in the regulation of chronic CNS inflammation. IFN-γ increases neuronal expression of MHC-I, which enhances cytotoxicity. In individuals with chronic sleep disturbances, IFN-γ levels rise in conjunction with REM sleep disruption, leading to persistent microglial activation and heightened neuroinflammation. This cytokine has been implicated in neuronal damage in Parkinson's disease and multiple sclerosis [18]. Targeting IFN-γ or its downstream signaling may represent a therapeutic approach in neurodegenerative diseases associated with sleep disturbances.

3.2 Key molecular pathways in neuroinflammation

In sleep disturbance induced neuroinflammation, the NF-κB, MAPK, and NLRP3 inflammasome signaling pathways are central to the pathophysiology of disorders such as Alzheimer's and Parkinson's disease. Disruption of REM sleep and chronic insomnia activate cytokine receptors such as TNFR and IL-1R, which trigger NF-κB signaling. Upon dissociation from its inhibitor, NF-κB translocates to the nucleus and upregulates pro-inflammatory genes including cyclooxygenase-2 (COX-2), TNF-α, inducible nitric oxide synthase (iNOS), and IL-6. As oxidative stress and mitochondrial dysfunction progress, the NLRP3 inflammasome complex becomes activated, leading to caspase-1 mediated maturation of IL-1β and IL-18, which amplifies the inflammatory cascade [19,20].

The MAPK pathway including its c-Jun N-terminal kinases (JNK), p38, and extracellular-signal-regulated kinase (ERK1) and ERK2 branches is also activated in response to these stimuli. ERK signaling is generally associated with cell survival, whereas activation of JNK and p38 promotes inflammation, apoptosis, and neuronal injury. Together, these pathways drive chronic microglial activation, increase blood-brain barrier (BBB) permeability, and ultimately accelerate neurodegeneration in the context of sleep disturbances [21].

4. Sleep disturbances, amyloid and tau pathology

Sleep disturbances including reduced slow-wave (deep) sleep and REM sleep disruption are recognized as independent risk factors for neurodegenerative pathologies, particularly Alzheimer's disease. Imaging studies and clinical data indicate that even subtle reductions in sleep quality can lead to increased β-amyloid (Aβ) deposition in brain regions such as the frontal cortex and hippocampus. The glymphatic clearance system, which becomes highly active during deep sleep, plays a critical role in removing neurotoxic proteins such as Aβ and Tau from the interstitial space. Inadequate or disrupted sleep impairs this clearance mechanism, resulting in chronic accumulation of these proteins [22]. Sleep deprivation also induces abnormal Tau phosphorylation, facilitating the spread of tauopathy across neural circuits. Remarkably, CSF levels of both Aβ and Tau have been shown to rise significantly after just a single night of sleep deprivation. Emerging evidence suggests a bidirectional relationship between sleep quality and amyloid/Tau pathology: sleep disruption increases Aβ and Tau levels, while the accumulation of these proteins further disrupts sleep particularly by affecting the thalamus and brainstem regions [23]. Beyond Alzheimer's and Parkinson's disease, other neurodegenerative disorders influenced by circadian rhythm disruption include Huntington's disease (HD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), multiple system atrophy (MSA), and spinocerebellar ataxia (SCA) [24]. Figure 2 illustrates the impact of circadian rhythm dysregulation on the progression of neurodegenerative diseases.

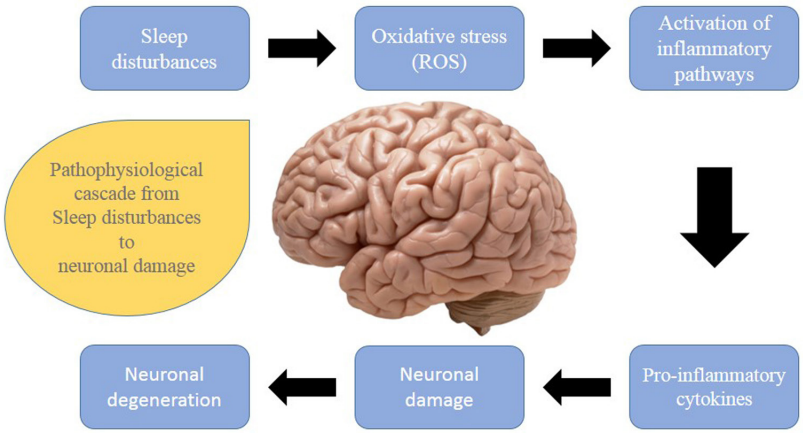

Figure 2. The role of circadian rhythm disorders and circadian clock-related genes (CLOCK, BMAL1, PER, and others) in various neurological diseases. Disorders of these molecular pathways are associated with the pathogenesis and clinical symptoms of neurodegenerative and motor diseases, including Parkinson's, Huntington's, cerebellar ataxia, multiple sclerosis, amyotrophic lateral sclerosis, and Alzheimer's.

5. Therapeutic outlook and research gaps

Despite significant progress in understanding the relationship between sleep disorders and neurodegenerative diseases, several important research gaps remain. One key question is whether sleep disturbances are a primary cause of neurodegeneration through the activation of inflammatory pathways such as NF-κB and the NLRP3 inflammasome, or whether they arise as secondary consequences of neuronal damage [25,26]. Another major limitation is the lack of reliable biomarkers capable of simultaneously assessing sleep quality, neuroinflammatory activity, and disease progression, which has hindered the development of accurate diagnostic tools [27]. Moreover, most clinical research has focused on Alzheimer's disease and Parkinson's disease, leaving other conditions such as amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) relatively understudied. From a therapeutic perspective, pharmacological strategies such as melatonin and orexin antagonists have been investigated for circadian rhythm regulation, while light therapy and chronotherapy show promise in improving sleep architecture [26,27]. In parallel, anti-inflammatory approaches targeting pathways like NLRP3 are being developed, and non-pharmacological interventions including non-invasive brain stimulation and cognitive behavioral therapy for insomnia (CBT-I) are emerging as complementary options [26]. Nevertheless, large-scale, longitudinal clinical trials are urgently needed to determine the efficacy of these interventions and to establish the most effective timing of treatment across different stages of neurodegenerative disease [27].

5.1 Drugs targeting molecular pathways

In recent years, there has been growing interest in molecular pathway-based therapies that modulate specific signaling mechanisms underlying sleep disruption and neurodegeneration, rather than broadly suppressing CNS activity. For example: Orexin receptor antagonists (e.g., daridorexant, lemborexant) inhibit Orexin receptor type 1 (OX1R) and OX2R receptors in the hypothalamus, thereby improving sleep continuity and reducing nocturnal awakenings [28]. NLRP3 inflammasome inhibitors attenuate neuroinflammation linked to sleep disturbances and reduce Aβ and Tau accumulation [29]. MAPK and NF-κB pathway inhibitors including BAY11-7082 [30], curcumin [31], SB203580 [32], SP600125 [33], resveratrol [34], and celastrol [35] mitigate neuronal injury by suppressing pro-inflammatory cytokines such as TNF-α and IL-6. SB203580 and SP600125, two selective MAPK pathway inhibitors, have demonstrated the ability to reduce neuroinflammation and preserve synaptic integrity in animal models of Alzheimer's disease and insomnia [32,33]. Natural compounds such as curcumin and resveratrol possess multi-target actions, combining antioxidant effects with inhibition of inflammatory signaling pathways. Despite their promise, many of these agents currently lack food and drug administration (FDA) approval for the direct treatment of sleep disturbances [36].

5.2 The Role of melatonin in sleep regulation

Melatonin, a hormone secreted by the pineal gland at night, is the primary regulator of circadian rhythms and plays a central role in initiating and maintaining sleep. In patients with neurodegenerative disorders such as Parkinson's and Alzheimer's disease, melatonin secretion is reduced, disrupting circadian rhythms and exacerbating sleep disturbances. Administration of melatonin or melanotan 1 (MT1)/MT2 receptor agonists can help restore circadian rhythm homeostasis, improve metabolic processes, and facilitate the clearance of neurotoxic proteins such as Tau and Aβ collectively enhancing sleep quality. Following its secretion, melatonin binds to MT1 and MT2 receptors. MT1 receptor activation inhibits adenylyl cyclase, reducing cAMP production, while simultaneously activating phospholipase C (PLC), which increases inositol triphosphate (IP3) and diacylglycerol (DAG) levels, thereby enhancing intracellular signaling. While, MT2 receptor activation stimulates the guanylyl cyclase pathway, modulating cGMP levels, and can either inhibit or stimulate adenylyl cyclase activity. Melatonin also binds to MT3 receptors (quinone reductase 2; QR2) in the cytosol, where it exerts antioxidant effects by reducing oxidative stress. Furthermore, after entering the cell nucleus, melatonin interacts with nuclear receptors retinoid Z receptor (RZR)/RAR-related orphan receptors (RORs), modulating gene expression and influencing sleep, circadian rhythms, and other physiological processes [37,38] .

6. Research gaps: the need for multi-omics and human studies

Despite substantial progress in understanding the molecular mechanisms linking sleep disturbances to neurodegenerative diseases, many pathways remain poorly defined. Current knowledge is largely derived from animal and in vitro studies, which have limited translational value to human physiology. To elucidate the complex interplay between sleep disturbances and neurodegeneration, multi-omics approaches including genomics, transcriptomics, epigenetics, proteomics, and metabolomics should be employed. Additionally, well-designed longitudinal human cohort studies incorporating multi-level assessments (e.g., biomarkers of sleep quality, inflammation, and cognitive performance) are essential to validate experimental findings [39,40].

7. Future research directions

RNA-based therapeutics including RNA interference (RNAi), antisense oligonucleotides (ASOs), and mRNA-based strategies are emerging as promising tools

for selectively targeting inflammatory genes and pathways. In conditions associated with sleep disturbances, these technologies hold potential for silencing genes involved in microglial activation, such as NLRP3 and triggering receptor expressed on myeloid cells 2 (TREM2), or for regulating cytokine expression [41,42]. In parallel, artificial intelligence (AI) offers powerful tools for analyzing complex datasets obtained from electroencephalography (EEG) recordings, actigraphy, and multi-omics platforms, enabling the discovery of hidden patterns underlying sleep disruption and neurodegenerative progression. AI can also accelerate drug discovery by identifying bioactive compounds from large chemical databases [43].

8. Conclusion

Sleep disturbances including insomnia and insufficient sleep aggravate neurodegenerative diseases by driving neuronal injury through multiple molecular pathways, such as oxidative stress, microglial activation, chronic neuroinflammation, and impaired clearance of pathogenic proteins (Tau and Aβ). Key signaling pathways involved in this process include NF-κB, MAPKs, and the NLRP3 inflammasome, which promote the release of pro-inflammatory cytokines such as IL-6 and TNF-α. Future therapeutic strategies should focus on targeted molecular pathway inhibition, antioxidants with high blood-brain barrier permeability, and circadian rhythm regulators (e.g., melatonin in combination with orexin receptor antagonists). Next-generation personalized interventions will integrate multi-omics profiling to identify sleep inflammation biomarkers and RNA-based therapeutics to modulate pathogenic gene expression. In the near future, AI-driven prediction models will enable early detection of sleep related neurological disorders and guide the development of precision therapeutics.

Authors' contributions

Conceptualization: NK, MAB, HH. Data curation: SHA, HH, PH, SA. Investigation: HH, PH, SA. Methodology: NK, SHA, HH, MAB. Original draft preparation: NK, SHA, MAB, PH, SA. Critical revision and editing: HH. All authors read and approved the final version of article.

Conflict of interest

No potential conflict of interest was reported by the authors.

Ethical declarations

Not applicable.

Financial support

Self-funded.

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