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Linking Sleep Deprivation to Neuronal Injury: A Review of Microglial and Glia-Mediated Mechanisms

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Abstract

Introduction: Sleep deprivation is rapidly emerging as a critical factor in accelerating neurodegeneration, as it is becoming recognized as a key cause of cognitive decline and neurodegeneration. This review examines the complex relationship between prolonged wakefulness, microglial activation, and neuronal injury. It discusses the central role of glial-mediated immune responses in sleep-deprived brain pathology, drawing on various research studies. **Methods:** A comprehensive literature review was conducted using PubMed, Scopus, and Google Scholar. Peer-reviewed, open-access articles published in English from 2011 to 2022 were included. The review examines how the pathways of inflammation, oxidative stress and excitotoxicity are mediated by microglia in stress, culminating in synaptic and neuronal loss. Some of the various triggers to microglial dysfunction are discussed, including TREM2-dependent impairment of Amyloid-beta clearance and the impact of CRH-mediated HPA axis activation. Furthermore, the cross-talk between astrocytes and microglia highlights how glial overload contributes to lysosomal dysfunction and chronic inflammation. **Results:** The review identified strong evidence linking sleep deprivation to heightened microglial activation, increased pro-inflammatory cytokine release, and oxidative stress, all contributing to neuronal and synaptic loss. Studies showed that disrupted TREM2 signaling impairs Amyloid-beta clearance, while HPA axis overactivation intensifies microglial-mediated neuroinflammation. Cross-talk between astrocytes and microglia under prolonged wakefulness was found to exacerbate lysosomal dysfunction and chronic inflammation. These findings were particularly pronounced in models of Alzheimer's disease, where sleep loss accelerated amyloid deposition and tau pathology. Experimental interventions targeting glial modulation and glymphatic function demonstrated potential neuroprotective effects. **Discussion:** The findings highlight the pivotal role of microglial dysfunction in the neuropathological consequences of sleep deprivation. Chronic sleep loss activates glial-mediated immune responses, disrupts clearance mechanisms, and fosters a neuroinflammatory environment conducive to synaptic degradation and neuronal injury. These mechanisms are particularly relevant in neurodegenerative diseases such as Alzheimer's, where impaired glial regulation correlates with accelerated plaque accumulation and tau pathology. **Conclusion:** This review underscores sleep deprivation as a modifiable risk factor for neurodegeneration, primarily through glial dysregulation. Targeting microglial and astrocytic pathways, enhancing glymphatic clearance, and reducing oxidative stress may offer promising neuroprotective strategies. Further translational research is essential to develop clinically viable interventions.

Keywords: Sleep deprivation, neurodegeneration, inflammation, oxidative stress and excitotoxicity, microglia, neuronal loss.

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აბსტრაქტი

შესავალი: უძილობა სწრაფად ხდება ნეიროდეგენერაციის დაჩქარების კრიტიკული ფაქტორი, რადგან იგი ცნობილია როგორც კოგნიტური უნარების დაქვეითებისა და ნეიროდეგენერაციის ერთ-ერთი მთავარი მიზეზი. ეს მიმოხილვა იკვლევს ხანგრძლივი ფხიზლობის, მიკროგლიის აქტივაციისა და ნეირონული დაზიანების შორის რთულ ურთიერთობას. განხილულია გლიური უჯრედების მიერ მართულ იმუნურ პასუხთა ცენტრალური როლი ძილის დანაკლისით გამოწვეულ ტვინის პათოლოგიებში, სხვადასხვა კვლევის მონაცემებზე დაყრდნობით. **მეთოდები:** ჩატარდა კომპლექსური ლიტერატურის მიმოხილვა PubMed, Scopus და Google Scholar-ის გამოყენებით. შესწავლილი იქნა 2011-2022 წლებში გამოქვეყნებული რეცენზირებული, ღია წვდომის მქონე ინგლისურენოვანი სტატიები. მიმოხილვა აჩვენებს, თუ როგორ მართავს მიკროგლია ანთების, ოქსიდაციური სტრესისა და ექსციტოტოქსურობის მექანიზმებს სტრესის პირობებში, რაც საბოლოოდ იწვევს სინაფსურ და ნეირონულ დანაკარგს. განხილულია მიკროგლიის დისფუნქციის რამდენიმე გამომწვევი ფაქტორი, მათ შორისაა TREM2-ით დამოკიდებული ამილოიდ-ბეტას კლირენსის დარღვევა და CRH-ის გავლენა ჰიპოთალამო-ჰიპოფიზურ-თირკმელზედა ღრუს (HPA) ღერძის გააქტიურებაზე. აგრეთვე, ასტროციტებსა და მიკროგლიას შორის ორმხრივი კავშირი ცხადყოფს, თუ როგორ უწყობს გლიური გადატვირთვა ხელს ლიზოსომული დისფუნქციისა და ქრონიკული ანთების განვითარებას. **შედეგები:** მიმოხილვამ გამოავლინა სარწმუნო მტკიცებულებები, რომლებიც აჩვენებს, რომ ძილის დანაკლისი უკავშირდება მიკროგლიის გააქტიურებას, პროანთებითი ციტოკინების გაძლიერებულ გამოყოფასა და ოქსიდაციურ სტრესს — რაც ხელს უწყობს ნეირონული და სინაფსური დაზიანებას. კვლევებმა აჩვენა, რომ TREM2-ის სიგნალიზაციის დარღვევა ამილოიდ-ბეტას კლირენსის დაქვეითებას იწვევს, მაშინ როცა HPA ღერძის ჰიპერაქტივაცია აძლიერებს მიკროგლიის მედიირებულ ნეიროანთებას. ასტროციტებისა და მიკროგლიის შორის კოაქტივაციამ ხანგრძლივი ფხიზლობის პირობებში გაზარდა ლიზოსომული დისფუნქცია და ქრონიკული ანთება. ეს პროცესები განსაკუთრებით თვალსაჩინო იყო ალცჰაიმერის დაავადების მოდელებში, სადაც ძილის დარღვევამ დააჩქარა ამილოიდური ფოლაქების დაგროვება და ტაუ პათოლოგიის განვითარება. გლიური მოდულაციისა და გლიმფატიკური ფუნქციის გაუმჯობესების მიმართულებით ექსპერიმენტულმა ჩარევებმა აჩვენეს პოტენციური ნეიროპროტექტორული ეფექტები. **განხილვა:** მიგნებები წარმოაჩენს მიკროგლიის დისფუნქციის გადამწყვეტ როლს უძილობის ნეიროპათოლოგიურ შედეგებში. ქრონიკული ძილის დანაკლისი ააქტიურებს გლიური იმუნური რეაქციებს, არღვევს ნარჩენების გაწმენდის მექანიზმებს და ქმნის ანთებით გარემოს, რომელიც ხელს უწყობს სინაფსურ დაშლასა და ნეირონულ დაზიანებას. ეს მექანიზმები განსაკუთრებით აქტუალურია ნეიროდეგენერაციულ დაავადებებში, როგორიცაა ალცჰაიმერის დაავადება, სადაც გლიური რეგულაციის დარღვევა კორელაციაშია ფოლაქების დაგროვების დაჩქარებასა და ტაუ პათოლოგიასთან. **დასკვნა:** ეს მიმოხილვა კიდევ ერთხელ უსვამს ხაზს უძილობის როლს როგორც ნეიროდეგენერაციის მოდიფიცირებად რისკ-ფაქტორს, რომელიც მოქმედებს გლიური დისრეგულაციის გზით. მიკროგლიური და ასტროციტული გზების მოდულაცია, გლიმფატიკური გაწმენდის გაუმჯობესება და ოქსიდაციური სტრესის შემცირება შეიძლება გახდეს პერსპექტიული ნეიროპროტექტორული სტრატეგიები. აუცილებელია შემდგომი ტრანსლაციური კვლევები ეფექტიანი კლინიკური ინტერვენციების განვითარებისთვის.

საკვანძო სიტყვები: ძილის უკმარისობა, ნეიროდეგენერაცია, ანთება, ოქსიდაციური სტრესი და ექსციტოტოქსიკურობა, მიკროგლია, ნეირონების დაკარგვა.

ციტატა: ჯაქვინ ჟოზე მალიილ, სოფიო ტატიშვილი. ძილის დარღვევის კავშირი ნეირონების დაზიანებასთან. მიკროგილიისა და გლიის გააქტიურებით განპირებული მექანიზმების მიმოხილვა. ჯანდაცვის პოლიტიკა, ეკონომიკა და სოციოლოგია. 2025; 9 (2). DOI: https://doi.org/10.52340/healthecosoc.2025.09.02.04.

Introduction

Sleep is an essential biological activity that regulates physiological and cognitive activities. The fundamental objective of this review is to study the processes by which sleep deprivation (going to be addressed as SD from henceforth) causes neuronal injury, with a particular emphasis on the involvement of microglial activation. Microglia, CNS-resident immune cells, contribute significantly to neurodegenerative mechanisms by clearing synaptic debris and releasing neurotoxic chemicals when activated excessively. (Colonna & Butovsky, 2017; Qin et al, 2023).

Various sleep deprivation studies establish the link between poor sleep and a variety of illnesses, including elevated blood pressure, weight gain and diabetes, cardiovascular disease and reduced immunological function (Worley, 2018). There are three major harmful processes caused by microglia under SD: inflammatory, oxidative, and excitotoxic mechanisms (Cai et al, 2022; Colonna & Butovsky, 2017). Consistent with these findings, multiple investigations have supported with evidence the involvement of pro-inflammatory cytokine release, oxidative stress with subsequent mitochondrial dysfunction, and an imbalanced synaptic transmission resulting in excitotoxicity (Colonna & Butovsky, 2017). The cumulative effects of these pathways contribute to long-term neuronal damage and predispose the brain to neurodegenerative diseases (Cai et al, 2022).

Additionally, the review examines how these pathways interact via microglial activation, regulating synaptic pruning and neuronal degeneration. Understanding the multifactorial processes underlying sleep deprivation-induced neuronal damage is crucial for future research and developing targeted therapeutic interventions.

Research problem: Gaps in the understanding of microglial activation patterns, along with limited insight into related pathways such as oxidative stress-induced neuronal damage, collectively contribute to the exacerbation of neuronal damage.

Modern lifestyles have contributed to turning sleep deprivation and prolonged wakefulness into a widespread phenomenon. The aim of this research is to critically evaluate the mechanisms by which sleep deprivation contributes to neuronal damage, find the links between various pathways and introduce preventive solutions.

Literature Review

Sleep Deprivation and Neuroglial Environment

Sleep deprivation is more than just a lack of sleep; it is a situation that sets off a chain reaction of molecular and cellular events that impact neurons (Worley,2018). Several studies have found substantial alterations in brain homeostasis following extended durations of wakefulness. Sleep loss, both acute and chronic, can alter microglial morphology, elevate pro-inflammatory mediators, and cause synaptic remodeling. SD affects both synaptic plasticity and immune cells in the brain, which contribute to neurodegenerative disorders (Worley, 2018).

SD can be divided into two. When there is a short-term period of insufficient sleep or no sleep lasting around 24 to 48 hours, it is called acute sleep deprivation (ASD). It becomes chronic sleep deprivation (CSD) when there is less than 7 hours per night for multiple consecutive nights (Worley, 2018).

SD activates microglia through multiple interconnected mechanisms, as below: TREM2-Dependent Microglial Activation [CSD]

The study found that chronic sleep deprivation not only stimulates microglia but also impairs their ability to remove Amyloid-beta deposits (Parhizkar et al, 2023). Sleep loss in mouse models, specifically the 5xFAD model of cerebral amyloidosis, was linked to aberrant lysosomal architecture and a reduction in microglia cleaning function for Amyloid-beta clearance (Parhizkar et al, 2023). This impairment is intimately connected to the TREM2 pathway, suggesting that activated microglia and related chronic SD may indirectly contribute to the neurodegenerative cascade observed in diseases like Alzheimer’s (Parhizkar et al, 2023).

Parhizkar et al, 2023, stated ***that*** chronic sleep deprivation enhances microglial reactivity via TREM2 signaling pathways. This activation occurs independently of amyloid-beta plaque presence, indicating that sleep loss alone can trigger microglial activation.

CRH-Mediated Mechanisms [CSD]

Sleep disturbances extend their impact beyond metabolic and synaptic processes by engaging the body's stress response system. In particular, the hypothalamic-pituitary-adrenal (HPA) axis and the associated release of corticotropin-releasing hormone (CRH) play critical roles in mediating neuroinflammatory responses via microglial activation (Guo et al, 2022).

Models of chronic sleep fragmentation show that increased CRH levels in the hippocampus trigger microglial activation. (Guo et al, 2022) CRH, a key mediator of the HPA axis response, activates galectin 3 in microglia, disrupting autophagy by impairing lysosomal membrane integrity (Guo et al, 2022). The release of lysosomal enzymes caused by this rupture impairs the regular turnover of damaged proteins and organelles, worsening neuronal stress and damage (Guo et al, 2022).

Disrupted CX3CR1 signaling [ASD & CSD]

The study by Xin J et al 2021, discussed C3 complement factor involvement in microglia-mediated synaptic pruning post sleep deprivation. The results of the study indicated that CX3CR1 has a pivotal function in modulating the neurological reaction to SD and the interaction of environmental stimuli and brain function, and its absence aids in the recovery from insomnia-related cognitive deterioration. (Xin J et al 2021)

Table: Overview of microglia activation pathways

Pathway	**Type of SD**	**Mechanism**	**Reference**
TREM 2 dependent	Chronic	Enhances microglial reactivity via TREM2, and Aβ plaques.	Parhizkar et al, 2023
CRH-mediated	Chronic	Elevated CRH in the hippocampus upregulates Galectin-3, impairing microglial lysosomes and activating microglia	Guo et al, 2022
Elevated Inflammatory Cytokines	Chronic	Increases IL-1β and TNF-α, activating microglia, contributing to neuroinflammation	Wisor et al, 2011
Mitochondrial Dysfunction and oxidative stress	Acute	Mitochondrial DNA release and oxidative stress trigger inflammation.	Hu et al, 2024
Disrupted CX3CR1 signaling	Acute, Chronic	Disruption of neuron-microglia signaling impairs synaptic pruning and activates microglia.	Xin J et al 2021
Altered microglial morphodynamics	Acute	Changes in process motility and surveillance capacity alter microglial morphology and activates them.	Hristovska et al, 2022
Impaired Autophagic and Lysosomal Pathways	Chronic	Impaired degradation pathways lead to cellular debris accumulation and microglial activation.	Parhizkar et al, 2023
Sustained microglial activation post sleep deprivation	Acute	Microglial activation persists even after recovery sleep.	Liu et al, 2023
Disruption of circadian clock genes	Chronic	Disrupts BMAL1 and REV-ER Bα expression, promoting neuroinflammation	Griffin et al, 2019

Pathways of Neuronal Damage in Sleep Deprivation

Microglial activation initiates primarily three pathways of neural damage. Additionally, crosstalk between glial cells can further amplify the neuronal damage, particularly through dysregulated interactions between microglia and astrocytes. These pathways are briefly described below:

- **Inflammatory Pathways:** Characterized by the enhancement of cytokines (Interleukin-1β, Tumor Necrosis Factor-α, Interleukin-6) and complement proteins, which contribute to a sustained inflammatory milieu (Cai et al, 2022).
- **Oxidative Stress:** Involves increased synthesis of ROS, lipid peroxidation, and mitochondrial DNA (mtDNA) damage that further exacerbate neuronal injury (Atrooz et al, 2019).
- **Excitotoxicity:** Results from excessive glutamatergic signaling, dysregulation of receptors, and imbalance of inhibitory and excitatory neurotransmission, ultimately leading to synaptic excitotoxic damage. (Nicosia et al, 2024; Colonna & Butovsky, 2017)
- **Cross-Talk Between Glial Cells**: During sleep deprivation, the interaction of astrocytes and microglia is critical (Carvalhas et at,2023). Initially, astrocytic phagocytosis functions as a protective mechanism, removing damaged synaptic components. However, continuous sleep deprivation exceeds astrocytes' compensatory capacities, resulting in chronic microglial activation (Bellesi et al, 2017). Persistent inflammation stresses neurons, leading to oxidative stress and toxic protein buildup, including beta-amyloid (Carvalhas et at, 2023).

Inflammatory Pathway: Microglial Activation and Cytokine release

Microglia are inherently highly motile cells with continuous monitoring activity (Carvalhas et at, 2023). Under standard conditions, they contribute to synaptic plasticity and debris clearance (Carvalhas et at, 2023). However, during sleep deprivation, these cells undergo significant morphological changes and become activated—a process marked by the upregulation of inflammatory mediators (Bellesi et al, 2017). Cytokines, mainly Interleukin-1β and 6, and Tumor Necrosis Factor-α are released by activated microglia (Bellesi et al, 2017). These cytokines potentiate the inflammatory response by further recruiting immune cells and activating local astrocytes, which can also become phagocytic under conditions of prolonged wakefulness. (Bellesi et al, 2017)

The priming that occurs due to sleep deprivation increases microglia’s sensitivity to secondary insults, such as amyloid deposition and environmental toxins. (Bellesi et al, 2017) Such changes corroborate that a prolonged inflammatory state may underlie the neural degeneration observed in conditions like Alzheimer’s disease (Bellesi et al, 2017).

Oxidative Stress and Lysosomal Dysfunction

The biochemical environment of sleep loss is further exacerbated by oxidative stress. ROS and lipid peroxidation can damage neuronal membranes and affect lysosomal integrity, as observed in investigations on astrocytic and microglial cells (Atrooz et al, 2019). The combination of oxidative stress and compromised autophagy mechanisms leads to the accumulation of cellular waste, rendering neurons more susceptible to injury (Atrooz et al, 2019).

Excitotoxicity: Complement Cascade Activation

Along with cytokine production, complement cascade is activated during the microglial response. (Bellesi et al, 2017) Chronic SD has been shown to significantly upregulate proteins such C3, which are part of the complement cascade. (Bellesi et al, 2017) Complement activation causes synaptic pruning, which is normally advantageous during development but can be harmful if it occurs abnormally in the human brain. (Bellesi et al, 2017) Overactivation of the complement system can lead to synapse loss, impairing cognitive activities and promoting neurodegeneration. (Bellesi et al, 2017)

TREM2 and Amyloid-β consequences

Inadequate clearance of Amyloid-beta can negatively impact neuronal health. Amyloid-beta plaques impede synaptic function, cause oxidative stress, and can lead to tau pathology, which is a characteristic of Alzheimer's disease. (Zhou et al, 2018) TREM2-dependent reduction in microglial cleaning function may synergize with additional SD-induced mechanisms, including as metabolic dysregulation and astrocytic overload, causing a complex vulnerability of neurons. (Zhou et al, 2018; Parhizkar et al, 2023).

Implications for Neurodegenerative Diseases and Potential Therapeutic Targets

Sleep deprivation causes significant cellular and molecular changes that have far-reaching implications in neural illnesses including Alzheimer's, Parkinson's, along with other cognitive dysfunctions. (Ahmadian et al, 2018) Chronic SD promotes the buildup of neurotoxic proteins such beta-amyloid-13 and primes the immune system to respond disproportionately to secondary insults through microglial activation. (Ahmadian et al, 2018)

Neurodegenerative Outcomes

The failure of proper Aβ clearance due to TREM2-dependent microglial dysfunction is a central pathway that links sleep loss and Alzheimer's disease emergence (Parhizkar et al, 2023). In parallel, CRH-mediated activation of microglia and the ensuing disruption in autophagy contribute to a neuroinflammatory environment that, over time, can lead to tau pathology and synaptic loss (Guo et al, 2022). Such processes have been correlated with declines in cognitive performance and memory impairment, as validated by both animal models and human studies. (Parhizkar et al, 2023)

Therapeutic Approaches:

Interventions aimed at mitigating SD-induced neuronal damage target multiple aspects of the pathology:

Enhancing Glymphatic Function: Strategies to boost glymphatic clearance may reduce the accumulation of beta-amyloid and other metabolites. Research has shown that exercise can accelerate glymphatic clearance and reduce amyloid-beta accumulation (Murdock et al, 2024). Studies have also shown that multisensory gamma stimulation and focused ultrasound treatment promote amyloid removal and stimulate glymphatic activity in mice. (Murdock et al, 2024)

Modulating Glial Activation: Pharmacological agents that regulate microglial activity—such as CRHR2 blockers to counteract CRH-mediated effects or compounds that restore TREM2 function—could help maintain a more homeostatic glial environment (Guo et al, 2022).

Discussion

Research papers highlight the complex lineage between neurodegeneration and sleep deprivation, focusing on the pivotal role played by microglial activation in mediating inflammatory, oxidative, and synaptic damage. Sleep deprivation initiates a cascade of pathological events, including the stimulation of inflammatory cytokine production, intensified reactive oxygen species activity, and altered glutamate stability. (Bellesi et al, 2017; Atrooz et al, 2019; Nicosia et al, 2024). The findings align with current literature that positions glial dysfunction, especially that of microglia, as a key contributor to neurodegenerative processes. (Colonna & Butovsky, 2017)

A central mechanism identified involves the TREM2 signaling pathway, which, when disrupted by chronic sleep loss, impairs microglial capacity to clear β-amyloid, thus facilitating amyloid plaque formation—a hallmark of Alzheimer's disease (Zhou et al, 2018). Simultaneously, CRH-induced microglial activation via the HPA axis highlights a systemic component to the localized neuroinflammatory process (Guo et al, 2022). This dual influence - one molecular and the other neuroendocrine - suggests that sleep deprivation primes microglia not only to initiate inflammation but also to respond aberrantly to subsequent neurotoxic challenges (Guo et al, 2022).

Furthermore, pertaining to the relationship between astrocytes and microglia, particularly in relation to chronic glial overload, accentuates the vulnerability of neurons under sustained wakefulness (Carvalhas et al, 2023). The astrocytic failure to regulate synaptic homeostasis leads to a chronic activation state in microglia, perpetuating low-grade inflammation and accelerating oxidative damage (Zhou et al, 2018). The review also emphasizes the breakdown of lysosomal and autophagic pathways, compounding neuronal stress and impairing cellular repair mechanisms. (Guo et al, 2022)

While this review synthesizes current knowledge effectively, limitations remain. First, a substantial portion of the cited research is based on animal models, limiting direct translation to human pathology. Additionally, the heterogeneity in experimental protocols, such as duration and type of sleep deprivation, introduces variability that complicates comparison across studies. The absence of long-term human data and the lack of consideration for sex and age-specific factors further constrain the potential of these results to be generalized. Further research ought to strive to include systematic reviews or meta-analyses, and encourage longitudinal clinical studies to strengthen causal conclusions.

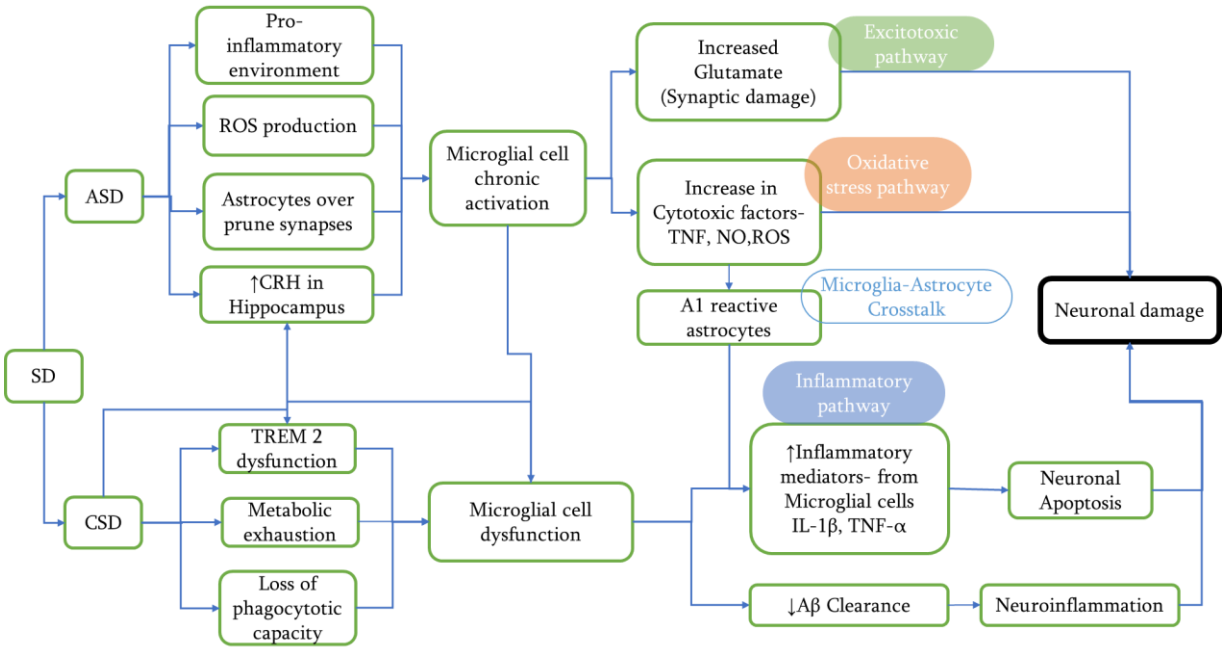

Figure 1: Overview of SD leading to Neuronal Damage.

Legend: SD: Sleep Deprivation; ASD: Acute Sleep Deprivation; CSD: Chronic Sleep Deprivation; CRH: Corticotropin-releasing Hormone; ROS: Reactive Oxygen Species; TREM: Triggering receptor expressed on myeloid cells; *Aβ: Amyloid beta; TNF: Tumor Necrosis Factor; NO: Nitric Oxide; IL-1β: Interleukin 1 beta*

Sleep deprivation, categorized as Acute or Chronic, initiates a cascade of pathophysiological processes that establishes a sustained state of neural activation. This environment is characterized by a proinflammatory milieu, excessive synaptic pruning mediated by astrocytes, and elevated levels of Corticotropin-releasing hormone (CRH). Their alterations are subsequently accompanied by TREM2 signaling dysfunction, metabolic compromise, and diminished phagocytic capacity of microglial cells. Collectively, these factors exert detrimental effects on microglial function, ultimately leading to the activation of neurotoxic cascades. These pathophysiological pathways include: Excitotoxic pathway characterized by glutamate accumulation and consequent synaptic injury; Oxidative stress pathway, involving the release of cytotoxic mediators such as tumor necrosis factor (TNF), nitric oxide (NO), and reactive oxygen species (ROS); and Inflammatory pathway, driven by the upregulation of proinflammatory cytokines and chemokines secreted by activated microglia. Impaired amyloid-beta clearance, resulting from microglial dysfunction, further exacerbates neuroinflammation through extracellular plaque buildup. These pathological mechanisms are further modulated by bidirectional glial cell interactions, particularly between microglia and astrocytes.

Conclusion

Sleep deprivation exerts profound effects on brain health by activating complex inflammatory, oxidative and metabolic pathways, predominantly mediated by glial cells (Parhizkar et al, 2023). Microglial activation, mainly through TREM2 and CRH signaling, disrupts essential functions such as synaptic pruning and Amyloid-beta (Aβ) clearance, resulting in persistent neuroinflammation (Guo et al, 2022; Zhou et al, 2018).

Cross-talk between astrocytes and microglia, coupled with oxidative stress, further exacerbates neurodegeneration. These findings highlight the pressing need to address sleep disturbances not only as lifestyle issues, but also as significant neurobiological challenges (Carvalhas et at,2023).

Therapeutic methods targeting glial modulation, glymphatic enhancement and oxidative damage mitigation may hold promise for mitigating the cognitive decline associated with chronic sleep loss. Further translational and clinical research is essential to validate these pathways and develop effective interventions.

By understanding the interdependent roles of the underlying pathways, and particularly the central involvement of microglial activation, researchers can better identify effective interventions to preserve

neuronal integrity. Future studies should continue to refine our knowledge of these mechanisms and integrate findings into medical practice with the ultimate goal of mitigating the risk of neurodegenerative disease.

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