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MINI-REVIEW

# The sleep–microbiome–neurodegeneration triad: A new frontier in neuroimmunology

**Gerardo Villalobos-Valdez†, Karyme M. Alemán-Villa†, David A. Armienta-Rojas, and Alberto K. De la Herrán-Arita***

Department of Neuroscience, Faculty of Medicine, Autonomous University of Sinaloa, Culiacán, Sinaloa, Mexico

## Abstract

The pathogenesis of neurodegenerative diseases is increasingly recognized as a systemic failure of homeostatic axes rather than a localized central nervous system event. Central to this paradigm is the "sleep–microbiome–neurodegeneration triad," a bidirectional framework where dietary inputs, gut microbial metabolites, and sleep architecture converge to regulate neuro–immune health. This mini review critically evaluates the evidence linking these domains, focusing on the mechanical and molecular bridges that facilitate their interaction. This mini review synthesizes data from recent (2015–December 2025) longitudinal clinical cohorts, metagenomic sequencing, and polysomnographic studies. We analyze the biochemical transition of dietary substrates, specifically the shift from fiber-derived short-chain fatty acids to ultra-processed food-induced endotoxemia, and relate these findings to neuroimaging evidence on glymphatic clearance efficiency. The evidence identifies a primary mechanistic "switch" in tryptophan metabolism. While fiber-rich diets promote microbial-led synthesis of serotonin and melatonin, the dysbiosis associated with Western diets upregulates the indoleamine 2,3-dioxygenase pathway. This reroutes tryptophan toward the kynurenine pathway, generating neurotoxic metabolites that correlate with sleep fragmentation. We further delineate how the resulting systemic inflammation primes microglial cells via toll-like receptor 4 signaling, concurrently disrupting slow-wave sleep. This disruption is shown to impair the aquaporin-4-dependent glymphatic system, leading to the reduced clearance of proteopathic aggregates, including β-amyloid and α-synuclein. This mini review proposes that the collapse of the sleep–microbiome–immune axis is a fundamental driver of proteinopathy. By characterizing these interactions, we identify modifiable metabolic checkpoints that offer novel targets for therapeutic intervention. Restoring this triad through precision nutrition and microbial modulation represents a vital strategy for stalling neurodegenerative progression.

***Keywords:*** Glymphatic clearance; Gut-brain axis; Kynurenine pathway; Neuroinflammation; Slow-wave sleep; Proteostasis

## 1. Introduction

The historical conceptualization of neurodegenerative diseases has undergone a fundamental shift, moving from a view of localized cerebral proteinopathies toward

†*These authors contributed equally to this work.*

***Corresponding author:**
Alberto K. De la Herrán-Arita
(alberto.kousuke@uas.edu.mx)

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a model of systemic homeostatic failure. While the accumulation of misfolded proteins, such as β-amyloid in Alzheimer's disease (AD) and α-synuclein in Parkinson's disease (PD), remains a pathological hallmark, the upstream drivers of these processes are increasingly found outside the central nervous system (CNS).[1] Central to this new paradigm is the "sleep–microbiome–neurodegeneration triad," a multi-organ axis where dietary patterns and gut microbial ecology significantly influence the efficiency of the brain's immune and clearance mechanisms.[2-4]

### 1.1. The nutritional–microbial nexus

Dietary intake serves as the primary substrate for the gut microbiota, acting as the fundamental "input" for the triad. The fermentation of complex polysaccharides by commensal taxa, particularly *Bifidobacterium* and *Faecalibacterium prausnitzii*, produces short-chain fatty acids (SCFAs) that maintain intestinal barrier integrity and modulate systemic immune tone.[3-5] Conversely, dietary patterns often termed the "Western diet," frequently characterized by high saturated fats and ultra-processed components, induce a state of chronic microbial dysbiosis[6] (Table 1). This shift facilitates the translocation of lipopolysaccharides (LPS) into systemic circulation, triggering a pro-inflammatory cascade that primes the blood–brain barrier (BBB) for increased permeability.[7]

**Table 1. Mechanistic "switches" within the sleep–microbiome–neurodegeneration triad**

| Physiological domain | Homeostatic state (fiber-rich) | Dysbiotic state (Western diet) | Supporting references |
|---|---|---|---|
| Metabolic output | High SCFA production (butyrate, acetate). | Increased LPS translocation and endotoxemia. | 5,6,8-10 |
| Tryptophan fate | Rerouted toward serotonin and melatonin. | Shunted to the kynurenine pathway via IDO-1. | 11-15 |
| Immune phenotype | Homeostatic microglial surveillance. | "Primed" hyper-reactive microglial phenotype. | 4,16-19 |
| Sleep architecture | Enhanced slow-wave sleep and delta power. | Sleep fragmentation and frequent arousals. | 20-24 |
| Brain clearance | Efficient AQP4-mediated glymphatic washout. | Mechanical "clogging" and protein retention. | 25-29 |

Abbreviations: AQP4: Aquaporin-4; IDO-1: Indoleamine 2,3-dioxygenase 1; LPS: Lipopolysaccharide; SCFA: Short-chain fatty acid.

Table 1 illustrates the biochemical and physiological transitions between homeostatic and dysbiotic states.

### 1.2. Sleep as the physiological mediator

The bridge between microbial signaling and neurodegeneration is largely constructed during sleep. Sleep is no longer viewed as a passive state of rest but as an active period of metabolic housekeeping.[25] Specifically, the discovery of the glymphatic system has revealed that the clearance of neurotoxic waste is highly dependent on slow-wave sleep (SWS), during which the expansion of the interstitial space allows for the aquaporin-4 (AQP4)-mediated washout of metabolic byproducts.[26] Evidence suggests that microbial metabolites, such as butyrate, directly promote the depth and duration of non-rapid eye movement (NREM) sleep, while dysbiosis-induced inflammation results in sleep fragmentation.[20,30]

### 1.3. The tryptophan–kynurenine "switch"

A critical biochemical intersection within this triad is the metabolic fate of dietary tryptophan. Under homeostatic conditions, tryptophan is utilized for the synthesis of serotonin and its derivative melatonin, the primary orchestrator of circadian rhythmicity.[11] However, under conditions of gut-derived systemic inflammation, the enzyme indoleamine 2,3-dioxygenase 1 (IDO-1) is upregulated, shunting tryptophan away from sleep-promoting pathways and toward the neurotoxic kynurenine pathway.[12] This metabolic diversion creates a self-perpetuating cycle: melatonin deficiency leads to sleep loss, which in turn impairs glymphatic clearance and accelerates the inflammatory priming of microglia.[21,31]

This mini review aims to synthesize recent evidence demonstrating that neurodegeneration is the downstream

consequence of the collapse of this triad. We evaluate how dietary modifications and microbial interventions may act as modifiable checkpoints to restore sleep architecture and enhance the brain's innate immune clearance. By mapping these pathways, we aim to provide a roadmap for early-stage intervention in the aging population.

## 2. The nutritional–microbial nexus: Upstream drivers

The structural integrity of the sleep–microbiome–neurodegeneration triad is primarily determined by dietary inputs, which serve as the substrate for microbial fermentation and metabolic signaling. Dietary patterns do not merely alter microbial diversity; they determine the biochemical "output" of the gut, which either stabilizes or destabilizes CNS homeostasis.[16]

### 2.1. Dietary fiber and the short-chain fatty acid–sleep connection

The fermentation of dietary fiber by anaerobic bacteria such as *Roseburia* and *Eubacterium rectale* generates SCFAs, primarily acetate, propionate, and butyrate.[8] These metabolites act as signaling molecules via G protein-coupled receptors (GPR41 and GPR43) located on the intestinal epithelium and the vagus nerve. Mechanistic studies have demonstrated that butyrate, in particular, exerts a sleep-promoting effect by modulating the expression of clock genes and enhancing the power of delta waves during NREM sleep.[22,25] Furthermore, SCFAs maintain the expression of tight-junction proteins (e.g., occludin and zonula occludens-1), thereby preventing the systemic translocation of neuroinflammatory triggers.[9]

### 2.2. The Western diet and metabolic endotoxemia

In contrast to fiber-rich patterns, the "Western" dietary profile, characterized by a high intake of saturated fats and ultra-processed carbohydrates, induces a rapid decline in microbial richness and an expansion of LPS-producing *Proteobacteria*.[32] Saturated fatty acids promote the emulsification of the intestinal mucus layer, allowing pathobionts to interact directly with the underlying immune cells of the lamina propria.[10] This process triggers "metabolic endotoxemia," a state of chronic, low-grade systemic inflammation characterized by elevated levels of circulating LPS. Once in circulation, LPS activates toll-like receptor 4 (TLR4) on peripheral immune cells and the vascular endothelium, signaling the brain to enter a state of "sickness behavior" characterized by fragmented sleep and inhibited glymphatic flow.[33]

### 2.3. Polyphenols and the "leaky" blood–brain barrier

Dietary polyphenols found in berries, green tea, and cocoa represent a potentially protective counter-regulatory mechanism. These compounds are metabolized by the gut microbiota into bioavailable phenolic acids that can cross the BBB.[34] Evidence suggests that these metabolites inhibit the activation of matrix metalloproteinases, which are responsible for degrading the BBB during inflammatory stress. By preserving the BBB, microbial-derived polyphenolic metabolites prevent the influx of neurotoxic cytokines that would otherwise disrupt the sleep–wake regulatory centers in the hypothalamus.[35]

## 3. The tryptophan–kynurenine "switch"

While the preservation of the BBB represents a structural defense, gut dysbiosis also fundamentally alters the brain's neurochemistry. The most direct molecular link within the triad is the metabolic fate of tryptophan, an essential amino acid and a precursor for both sleep-promoting and neurotoxic molecules. The "switch" between these pathways is heavily governed by the microbial environment.

### 3.1. Metabolic diversion and the indoleamine 2,3-dioxygenase pathway

Under healthy conditions, the majority of dietary tryptophan is utilized by the gut microbiota and host cells for the synthesis of serotonin, which is subsequently converted into melatonin in the pineal gland to regulate sleep onset.[13] However, microbial dysbiosis and the resulting inflammatory milieu upregulate the IDO-1 enzyme in both the gut and the brain[14] (Table 1). This enzyme shunts tryptophan away from the methoxyindole pathway (melatonin) and toward the kynurenine pathway (Figure 1).

### 3.2. Neurotoxicity and circadian misalignment

The activation of the kynurenine pathway produces a series of metabolites, including kynurenic acid and quinolinic acid. While kynurenic acid can be neuroprotective at physiological levels, chronic overproduction of quinolinic acid, an N-methyl-D-aspartate receptor agonist, leads to excitotoxicity and microglial activation.[36] From a chronobiological perspective, this "shunt" results in a systemic deficiency of melatonin. This deficiency not only impairs sleep initiation but also reduces the antioxidant capacity of the brain during the night, leaving neurons vulnerable to oxidative damage during periods of already compromised glymphatic clearance[15] (Figure 1).

## 4. Immune mediators: Microglial priming and toll-like receptor 4 signaling

The translation of peripheral microbial dysbiosis into central neurodegeneration is largely executed by the innate

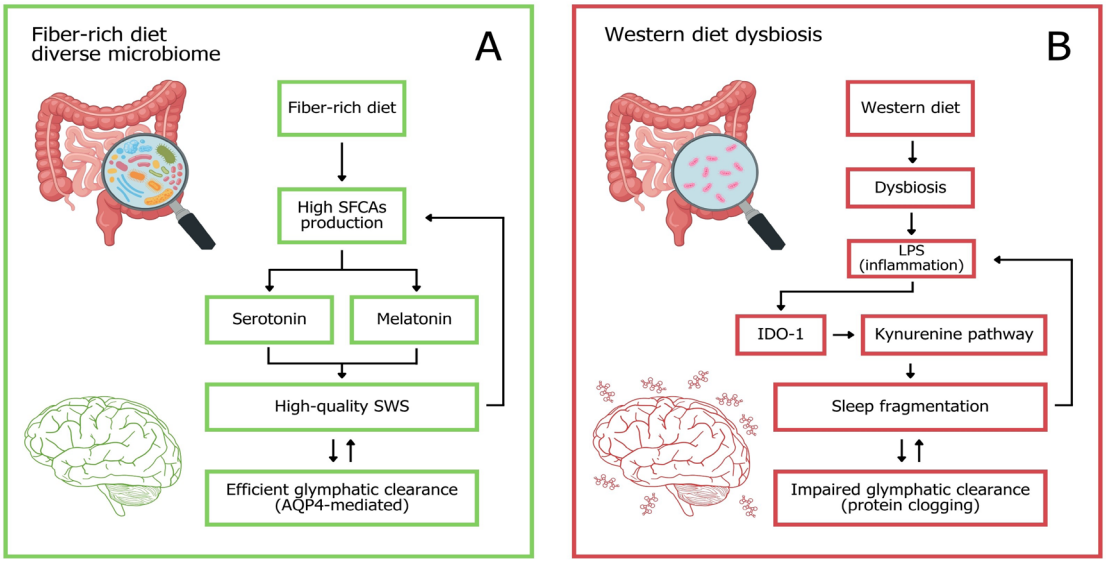



**Figure 1.** The sleep–microbiome–neurodegeneration triad: mechanistic pathways. (A) Homeostatic state: A fiber-rich diet promotes a diverse microbiome and the production of short-chain fatty acids (SCFAs), specifically butyrate. These metabolites facilitate the synthesis of serotonin and melatonin while maintaining intestinal barrier integrity. This environment supports high-quality slow-wave sleep (SWS), which optimizes aquaporin-4 (AQP4)-dependent glymphatic clearance, effectively flushing proteopathic aggregates (e.g., β-amyloid) from the brain parenchyma. (B) Dysbiotic state: The "Western diet" leads to microbial dysbiosis and increased levels of lipopolysaccharides (LPS), triggering systemic metabolic endotoxemia. Inflammation upregulates indoleamine 2,3-dioxygenase 1 (IDO-1), shunting tryptophan metabolism toward the kynurenine pathway and neurotoxic quinolinic acid. This biochemical shift drives sleep fragmentation and microglial priming (toll-like receptor 4 activation). The resulting loss of SWS impairs glymphatic efficiency, leading to "mechanical clogging" and the acceleration of neurodegenerative proteinopathies. Image created by the authors.

immune system. In this context, the immune system acts as a biological "interpreter," converting gut-derived metabolic signals into neuroinflammatory states that disrupt sleep and neuronal health.[17]

### 4.1. Peripheral-to-central signaling via toll-like receptor 4

The primary molecular bridge in this process is the activation of TLR4. While LPS is the most recognized ligand for TLR4, other microbial-associated molecular patterns resulting from a high-fat di*et al*so engage this receptor.[37] Chronic systemic exposure to LPS induces a persistent state of low-grade inflammation. Although the BBB limits the direct entry of large molecules, systemic cytokines like tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1β can alter BBB permeability or communicate with the CNS through the circumventricular organs and vagal afferents.[38] This signaling cascade initiates the transcriptional reprogramming of the brain's resident immune cells.

### 4.2. The "primed" microglial phenotype

Microglia, the primary immune effectors of the CNS, exist in a state of constant surveillance. However, chronic microbial-induced inflammatory signaling shifts these cells from a homeostatic state into a "primed" or hyper-reactive phenotype.[18] Unlike acute activation, microglial priming involves long-lasting epigenetic changes that lower the threshold for a secondary inflammatory stimulus. In the context of the triad, the microbial-induced "first hit" ensures that any subsequent challenge, such as the accumulation of Aβ or a period of sleep deprivation, triggers an exaggerated, neurotoxic release of reactive oxygen species and pro-inflammatory mediators.[39]

### 4.3. Cytokine-induced sleep architecture disruption

Immune signaling and sleep regulation share common molecular pathways. IL-1β and TNF-α are known somnogenic cytokines; at physiological levels, they regulate the homeostatic drive for SWS.[23] However, the pathological elevations seen in chronic gut dysbiosis lead to "sickness behavior" sleep patterns. This is characterized by increased sleep latency and frequent arousals, which prevent the brain from entering the deeper stages of NREM sleep required for metabolic recovery. This fragmentation creates a feedback loop: poor sleep further exacerbates microglial activation, which in turn continues to destabilize sleep architecture[24,40,41] (Table 1).

## 5. Sleep as a bridge: The glymphatic system

These immune-mediated disruptions to sleep architecture have downstream mechanical consequences. While the immune system provides the chemical bridge, sleep provides the mechanical bridge. The discovery of the glymphatic system has provided the "missing link" that explains why sleep disruption is a critical factor in the progression of proteinopathy.

### 5.1. The physiology of glymphatic clearance

The glymphatic system is a highly organized fluid transport pathway that facilitates the exchange of cerebrospinal fluid and interstitial fluid. This exchange is driven by the convective flow of cerebrospinal fluid into the brain parenchyma through peri-arterial spaces, a process mediated by the polarization of AQP4 water channels on astrocytic endfeet.[27] Crucially, this clearance mechanism is nearly ten times more active during SWS than during wakefulness, as the interstitial space expands during sleep to reduce resistance to fluid flow.[27,28,42,43]

### 5.2. The "clogging" hypothesis and proteinopathy

In the triad, sleep fragmentation, driven by the kynurenine pathway and microglial-derived cytokines, acts as a mechanical "clog" on this clearance system. Reduced time spent in SWS leads to parenchymal retention of metabolic waste products, including β-amyloid, tau, and α-synuclein[28,43,44] (Figure 1). Experimental models demonstrate that even acute sleep deprivation significantly increases the burden of these proteins in the interstitial fluid. Over time, this failure of clearance leads to the formation of the insoluble aggregates that define AD and PD.[19,45]

### 5.3. Influence of gut metabolites on astrocytic integrity

Emerging evidence suggests that the microbiome also influences the glymphatic system more directly. SCFAs, particularly butyrate, have been shown to modulate the expression and polarization of AQP4 on astrocytes.[46] Furthermore, microbial-derived indoles, products of tryptophan metabolism, activate the aryl hydrocarbon receptor on astrocytes, which helps suppress CNS inflammation and maintain the structural integrity of the glymphatic pathways.[47] Consequently, dysbiosis not only disrupts sleep–wake cycles but also compromises the very cellular architecture required for brain "washing."

## 6. Clinical integration: From dysbiosis to proteinopathy

The theoretical framework of the triad is supported by a growing body of clinical evidence linking specific microbial signatures to sleep disturbances and the hallmark pathologies of neurodegenerative diseases.

### 6.1. Alzheimer's disease: The amyloid–sleep–gut feedback loop

In patients with AD, a distinct reduction in the abundance of anti-inflammatory taxa, such as *Eubacterium rectale*, is consistently observed.[48] Clinical data indicate that this microbial depletion correlates strongly with increased cerebral amyloid burden as measured by positron emission tomography imaging. Mechanistically, this is facilitated by the loss of SCFA-mediated protection of the BBB. In AD cohorts, chronic sleep fragmentation is not merely a symptom but a predictive biomarker; reduced SWS duration precedes the clinical onset of memory impairment by years[48] (Table 2). We propose that in AD, the "clogging" of the glymphatic system by sleep loss represents a critical failure point at which microbial-induced neuroinflammation prevents the nocturnal clearance of Aβ and tau, leading to accelerated plaque deposition.[29,49-51]

Table 2 synthesizes the clinical evidence linking the triad to specific neurodegenerative pathologies and interventions.

### 6.2. Parkinson's disease: The "gut-first" model and alpha-synuclein

Parkinson's disease provides perhaps the most striking evidence for the triad. The "Braak hypothesis" suggests that α-synuclein pathology may originate in the enteric nervous system before ascending to the brain via the vagus nerve.[52] Patients with PD frequently present with intestinal hyperpermeability and a pro-inflammatory microbiota high in *Akkermansia* (which can degrade the mucus layer) and low in *Prevotella*[53] (Table 2).

Notably, rapid eye movement sleep behavior disorder is one of the strongest prodromal markers for PD. During these sleep disruptions, the lack of glymphatic "rinsing" may facilitate the aggregation of α-synuclein in the brainstem, specifically in areas regulating sleep and autonomic function, thereby locking the patient into a cycle of worsening dysbiosis and neurodegeneration.[54]

## 7. Therapeutic horizons and future directions

The modifiability of the triad offers a promising landscape for novel interventions that target the gut and sleep to protect the brain. It is important to acknowledge that aging involves a systemic, physiological decline in metabolic and signaling efficiency that cannot be entirely

**Table 2. Clinical hallmarks and therapeutic targets in neurodegenerative diseases**

| Disease context | Microbial signature | Sleep biomarker | Pathological consequence | Therapeutic target | Supporting references |
|---|---|---|---|---|---|
| Alzheimer's disease | Reduced anti-inflammatory taxa (e.g., *E. rectale*). | Chronic slow-wave sleep reduction; amyloid buildup. | Accelerated β-amyloid and tau deposition. | Precision psychobiotics; oligomannate. | 7,31,43,48, 49 |
| Parkinson's disease | High *Akkermansia; Low Prevotella*. | Rapid eye movement sleep behavior disorder. | α-synuclein aggregation (gut-first model). | Vagal modulation; butyrate restoration. | 52-55 |
| Aging/general | Loss of microbial richness; Proteobacteria. | Sleep latency; "sickness behavior" sleep. | Failure of aquaporin-4-dependent brain washing. | Chrononutrition; prebiotic fibers. | 32,37,46,51,56 |

halted. However, the interventions proposed here do not seek to stop biological aging, but rather to mitigate the pathological acceleration of this decline driven by dysbiosis. By maintaining microbial diversity and sleep integrity, therapeutic strategies aim to preserve the aging brain's compensatory mechanisms and extend the "healthspan" of the neuro–immune axis.

### 7.1. Precision psychobiotics and prebiotics

Targeted supplementation with specific bacterial strains, such as *Lactobacillus plantarum* and *Bifidobacterium longum*, has been shown to improve sleep quality and reduce systemic pro-inflammatory cytokines in elderly populations.[57] These "psychobiotics" may exert their effects by restoring the tryptophan–kynurenine balance, shifting metabolism back toward melatonin synthesis. Furthermore, high-solubility prebiotic fibers can enhance butyrate production, which directly stabilizes the astrocytic endfeet required for glymphatic flow.[55]

### 7.2. Chrononutrition and sleep hygiene

Emerging research into "chrononutrition" suggests that the timing of food intake is as critical as its composition. Aligning dietary patterns with the host's circadian rhythm may optimize the "metagenomic clock," ensuring that microbial metabolite production peaks in synchrony with the glymphatic clearance cycle.[56] Future clinical trials should focus on combined therapies, such as evening prebiotic intake coupled with blue-light restriction, to maximize the synergistic effects of the triad.

### 7.3. Limitations

While the "sleep–microbiome–neurodegeneration triad" offers a compelling framework, current evidence relies heavily on murine models to establish mechanistic causality. Human studies, though supportive, are largely observational and subject to the heterogeneity of dietary habits and genetic backgrounds. Furthermore, translating specific "psychobiotic" interventions from animal models to human clinical efficacy remains an area that requires rigorous longitudinal validation to distinguish between associative markers and causative drivers.

## 8. Conclusion

The sleep–microbiome–neurodegeneration triad represents a paradigm shift in our understanding of brain health. By characterizing neurodegeneration as the downstream consequence of a collapse in the gut–sleep–immune axis, we move away from reactive treatments and toward proactive, systemic prevention. The evidence synthesized in this mini review demonstrates that the brain does not age in isolation; its health is inextricably linked to the microbial ecology of the gut and the mechanical integrity of sleep-dependent clearance. Protecting the aging brain requires a holistic approach that prioritizes the restoration of this vital triad.

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## Conflict of interest

The authors declare that they have no competing interests.

## Author contributions

*Conceptualization:* Gerardo Villalobos-Valdez, Alberto K. De la Herrán-Arita
*Visualization:* All authors
*Writing–original draft:* All authors
*Writing–review & editing:* Karyme M. Alemán-Villa, Alberto K. De la Herrán-Arita

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