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Intestinal Permeability and Neuroinflammation: Physiopathological Connections

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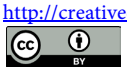

Abstract

The integrity of the intestinal barrier plays a crucial role in maintaining immune and metabolic homeostasis. Alterations in intestinal permeability, often described as "leaky gut", allow the translocation of microorganisms and their products, such as lipopolysaccharides, into systemic circulation. This process induces chronic low-grade inflammation with repercussions on the central nervous system. Growing evidence indicates that intestinal barrier dysfunction is closely linked to neuroinflammation through microglial and astrocytic activation, as well as modulation of the blood-brain barrier. These interactions contribute to the pathophysiology of neurodegenerative disorders, including Alzheimer's and Parkinson's diseases, in addition to psychiatric conditions such as depression and anxiety. Therapeutic strategies aimed at restoring intestinal integrity—including probiotics, prebiotics, anti-inflammatory diets, and pharmacological modulators—have shown potential in mitigating neuroinflammation. Understanding the pathophysiological connections between intestinal permeability and neural inflammation may open new avenues for preventive and therapeutic approaches in complex neurological conditions.

Keywords

Intestinal Permeability, Neuroinflammation, Gut-Brain Axis, Microbiota, Neurodegenerative Diseases

1. Introduction

Integrative medicine seeks not only to treat symptoms but also to identify and

mitigate the underlying factors contributing to persistent inflammation, such as blood-brain barrier dysfunction, mitochondrial imbalance and oxidative stress, and gut microbiota dysbiosis.

Communication between the gut and the brain occurs through various interconnected mechanisms, including the direct transport of metabolites and cytokines across the blood-brain barrier, activation of cerebral endothelial cells that release inflammatory mediators and alter barrier permeability, and neural signaling through the vagus nerve, which conveys intestinal stimuli to the central nervous system (CNS), modulating autonomic and inflammatory responses.

In clinical practice, neuroinflammation refers to the inflammatory response of the CNS triggered by various stimuli, such as infections, trauma, neurodegenerative diseases, ischemia, autoimmunity, or toxin exposure. This response is primarily mediated by the activation of glial cells (microglia and astrocytes) and the release of proinflammatory cytokines such as TNF-alpha and interleukins, which play a key role in mediating chronic inflammation that can lead to neuronal loss and synaptic dysfunction [1].

The gut-brain axis represents a bidirectional communication system connecting the gastrointestinal tract and the central nervous system [1]. The gut microbiota actively participates in this axis by modulating immunological, metabolic, and neuroendocrine processes. Alterations in intestinal permeability can disrupt this homeostasis, resulting in systemic inflammation and activation of neuroinflammatory pathways [2] [3]. In recent years, the concept that intestinal disturbances may contribute to neurological diseases has gained strong support in the literature [4] [5].

Several studies have shown that this peripheral inflammation can directly impact the CNS. Circulating proinflammatory cytokines and microbial products derived from the gut are capable of crossing or modulating the blood-brain barrier, activating glial cells, particularly microglia and astrocytes. This process contributes to the establishment and maintenance of a neuroinflammatory state, characterized by excessive production of inflammatory mediators within neural tissue. Neuroinflammation, in turn, is closely associated with the pathophysiology of various neurological conditions, including neurodegenerative diseases such as Alzheimer's and Parkinson's, as well as psychiatric disorders such as depression and anxiety.

Moreover, growing evidence suggests that intestinal permeability not only influences neural inflammation but may also precede and potentially exacerbate the progression of CNS disorders. The identification of biomarkers related to intestinal barrier dysfunction and their correlation with neurological alterations opens promising perspectives for the development of diagnostic and therapeutic strategies.

2. Methodology

2.1. Type of Study

This study is a narrative literature review aimed at gathering and discussing the

available scientific evidence on the relationship between intestinal permeability and the gut-brain axis, emphasizing the pathophysiological mechanisms and clinical implications of this interaction. This type of review was chosen because it allows for a broad, interpretative, and critical analysis of scientific findings, without the strict inclusion and exclusion criteria required in systematic reviews.

2.2. Data Sources and Search Strategy

The bibliographic search was conducted in the PubMed/MEDLINE, Scielo, Science Direct, and Google Scholar databases, considering publications from 2010 to 2025. The following controlled and uncontrolled descriptors, in Portuguese and English, were used and combined with Boolean operators: "Permeabilidade intestinal" OR "Intestinal permeability"; "Eixo intestino-cérebro" OR "Gut-brain axis"; "Neuroinflamação" OR "Neuroinflammation"; "Microbiota intestinal" OR "Gut microbiota"; "Tight junctions" OR "Junções oclusivas".

The search strategy followed the combination of terms: ("Intestinal permeability" AND "Gut-brain axis") OR ("Leaky gut" AND "Neuroinflammation").

2.3. Inclusion and Exclusion Criteria

Included materials consisted of original articles, reviews, dissertations, and book chapters addressing the relationship between intestinal barrier alterations, microbiota, and neuroinflammatory processes. Studies conducted in humans and animal models were included, provided they presented relevant pathophysiological insights into the topic.

Exclusion criteria comprised studies focused exclusively on gastrointestinal diseases without mention of the gut-brain axis, articles without full-text access, and publications in languages other than Portuguese, English, or Spanish.

2.4. Selection and Analysis of Studies

The selection of articles was performed in three stages:

1) Screening of titles and abstracts for initial relevance identification;

2) Full-text reading of the selected studies;

3) Qualitative and integrative analysis of results, grouping findings into thematic axes:

- Pathophysiological mechanisms of intestinal permeability;
- Role of gut microbiota in the modulation of the gut-brain axis;
- Relationship between intestinal permeability and neuroinflammation;
- Clinical and therapeutic implications.

The discussion of results was conducted in a critical and interpretative manner, based on the convergence and divergence among the findings of different studies.

3. Mechanisms of Neuroinflammation

Integrative medicine represents a broad and interdisciplinary approach to human health, assessing the health-disease process through the understanding that bio-

logical, psychological, and environmental factors interact dynamically and continuously. From this perspective, the therapeutic objective transcends mere symptom control, prioritizing the identification and correction of the underlying pathophysiological mechanisms that contribute to low-grade chronic inflammation—one of the main etiopathogenic pathways of various noncommunicable chronic diseases.

Blood-brain barrier dysfunction, mitochondrial dysfunction, oxidative stress, and gut microbiota imbalance are common causes of systemic chronic inflammation and, consequently, contribute to neuroinflammation. Persistent activation of microglia and astrocytes, as well as infiltration of peripheral immune cells into the CNS, sustain an inflammatory cycle that, when chronic, leads to neuronal degeneration typical of neurological diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS), and multiple sclerosis [5] [6].

4. Clinical Implications

Neuroinflammation is closely linked to the progression of several neurodegenerative diseases. In Alzheimer's disease, for example, the accumulation of beta-amyloid plaques and neurofibrillary tangles triggers microglial activation, leading to an inflammatory cascade that worsens neuronal degeneration. Similarly, in Parkinson's disease, chronic microglial activation contributes to the death of dopaminergic neurons, exacerbating the characteristic motor symptoms of the condition.

In clinical practice, the groups of patients most affected by neuroinflammation include those with neurodegenerative diseases, neuroimmune disorders, specific psychiatric conditions, and infections of the central nervous system (CNS).

Among neurodegenerative diseases, patients with Parkinson's disease and atypical parkinsonian syndromes such as progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) exhibit distinct patterns of neuroinflammation. In PSP, there is a more intense T-cell-mediated inflammatory response, whereas in Parkinson's disease, microglial activation predominates. The intensity of neuroinflammation tends to be higher in the early stages of these diseases, declining as neuronal loss becomes more advanced [7].

Patients with neuroimmune disorders, such as multiple sclerosis (MS), neuromyelitis optica, autoimmune encephalopathies, and acquired demyelinating syndromes, are also strongly affected by neuroinflammation. In these cases, there is local cytokine production in the cerebrospinal fluid (CSF), increased numbers of B and NK cells, and elevated inflammatory markers, particularly when the blood-brain barrier is intact or disrupted [7] [8]. In addition, bacterial and viral infections of the CNS, such as meningitis and Lyme neuroborreliosis, are associated with significant elevations in cytokines and inflammatory cells in the CSF [8].

In the psychiatric context, subgroups of patients with schizophrenia and other psychotic disorders exhibit elevated peripheral inflammatory profiles associated

with functional alterations in brain networks and poorer cognitive performance. These subgroups can be identified by markers such as IL-6, IL-8, IFN-γ, and C-reactive protein (CRP), and show distinct patterns of gray matter volume reduction and neurocognitive deficits [9]. Patients with recent-onset depression, especially in more severe cases, also display increased neuroinflammatory biomarkers in the CSF, such as elevated total leukocyte counts, suggesting neuroimmune activation.

Intestinal barrier dysfunction has been identified as a potential source of the peripheral inflammation observed in neuropsychiatric conditions such as depression and schizophrenia. Increased intestinal permeability allows the translocation of microbial components, such as lipopolysaccharides, into the systemic circulation, triggering immune responses and releasing proinflammatory cytokines. This peripheral inflammation may, in turn, compromise the integrity of the blood-brain barrier and induce neuroinflammatory processes, establishing a connection between intestinal dysfunction and the brain alterations associated with these disorders.

Biomarkers are essential tools for the detection and monitoring of neuroinflammation, serving as indicators of disease presence and progression. Fluid biomarkers, such as those found in serum and cerebrospinal fluid, have gained significant attention due to their ability to reflect neuroinflammatory changes in a minimally invasive way.

The relevance of studying biomarkers in neuroinflammation cannot be overstated, as they provide critical insights into the pathophysiology and potential treatment of CNS disorders. Their ability to indicate inflammatory and neurodegenerative responses grants them potential as therapeutic targets. This research field is particularly promising because it paves the way for personalized medicine, in which treatments are tailored according to patients' individual biomarker profiles.

In Alzheimer's disease–related neuroinflammation, recent studies—such as those published in *The Journal of Prevention of Alzheimer's Disease*—have highlighted the importance of biomarkers like neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) as diagnostic and prognostic tools. When measured in plasma and cerebrospinal fluid, these biomarkers have proven effective in detecting neuroinflammatory alterations that precede the visible clinical symptoms of Alzheimer's disease.

Additionally, inflammatory biomarkers in blood, such as C-reactive protein (CRP), have been investigated in mood disorders, providing an important link between peripheral inflammation and structural brain changes observed through neuroimaging techniques like magnetic resonance imaging (MRI). Studies have revealed that high CRP levels are associated with cortical thinning and reduced gray matter volume in critical brain regions such as the prefrontal cortex, supporting the hypothesis that systemic inflammation contributes to neurodegeneration.

Finally, research on the relationship between neuroinflammatory biomarkers

and Lewy body dementia has also been conducted. According to systematic reviews, the analysis of differentially expressed proteins in brain tissues from individuals with Lewy body dementia highlights the importance of biomarkers such as taus and GFAP in the molecular pathology of the disease, underscoring their potential as targets for innovative therapies.

5. Therapies for Modulating Neuroinflammation

Pharmacological interventions aimed at modulating microglial activity and reducing neuroinflammation have been an area of intense research. Anti-inflammatory agents, immunomodulators, and stem cell-based therapies are among the approaches being investigated to counteract the adverse effects of neuroinflammation on the central nervous system (CNS).

Given the complexity of neuroinflammation, integrative practice employs strategies such as targeted nutritional supplementation, probiotic-based therapies, stress-reduction techniques, and anti-inflammatory dietary interventions. Evidence suggests that integrative approaches may help control the inflammatory process and improve mental and cognitive health parameters, providing additional support to traditional pharmacological therapies. This integrative model reinforces the need for personalized treatment plans that consider each patient's unique profile to optimize the clinical management of neuroinflammatory conditions.

Nutritional supplementation has therefore emerged as a promising approach to mitigate neuroinflammation—a condition associated with various neurological and psychiatric disorders. The growing understanding of the relationship between diet, inflammation, and brain health has encouraged the exploration of nutritional supplements as potential therapeutic interventions. Among them, nutrients such as vitamin D, omega-3 fatty acids, probiotics, and plant-derived bioactive compounds have demonstrated anti-inflammatory and neuroprotective effects in both preclinical and clinical studies.

6. Natural and Synthetic Antioxidants: Current Clinical Evidence

Antioxidant therapy, using both natural and synthetic compounds, has become a relevant strategy for modulating neuroinflammation and oxidative stress—central processes in neurodegenerative diseases. These agents can be categorized according to their main mechanisms of action:

1) neutralizers of reactive species and mitochondrial protectors;

2) immunoinflammatory modulators; and

3) metabolic and synaptic regulators.

Antioxidants act by neutralizing reactive species and modulating inflammatory pathways. Natural compounds such as resveratrol, curcumin, quercetin, and other flavonoids activate Nrf2 and inhibit NF-κB, promoting mitochondrial protection and reducing oxidative stress [10].

Coenzyme Q10 (CoQ10): In addition to its classical role in the mitochondrial electron transport chain, CoQ10 exerts antioxidant and anti-inflammatory actions, regulates mitochondrial homeostasis, and stabilizes mitochondrial dynamics. In neurological diseases, it has demonstrated neuroprotective effects in experimental models, and recent reviews highlight its potential in Parkinson's disease, Alzheimer's disease, multiple sclerosis, ataxias, and other conditions [11]. Preclinical studies show that CoQ10 can modulate NF-κB to reduce brain inflammation [12]. However, in meta-analyses of clinical trials in Parkinson's disease, functional benefits remain unclear—although formulation and bioavailability issues may influence outcomes [13].

Omega-3 (n-3 polyunsaturated fatty acids): Recent meta-analyses in individuals without dementia suggest a dose-dependent effect on cognitive function, particularly in long-term interventions [14]. Conversely, in patients with Alzheimer's disease, omega-3 supplementation has not shown statistically significant cognitive improvement in some controlled trials [15]. There is also evidence that the effect may depend on baseline "omega-3 index," suggesting individual variability in response.

Vitamin D: As an immune modulator, vitamin D acts through VDR receptors in neural and immune cells, promoting anti-inflammatory and neurotrophic effects. In multiple sclerosis, meta-analyses of RCTs have shown that vitamin D supplementation is associated with reduced relapse rates, fewer new T2 lesions, and mild improvement in disability scores [16].

N-acetylcysteine (NAC): NAC, a cysteine donor for glutathione (GSH) synthesis, improves redox homeostasis and modulates intracellular inflammation. Although extensive preclinical evidence supports its role in mitochondrial protection and suppression of inflammatory pathways (such as NF-κB), more robust clinical trials are still needed to determine its systematic impact on neurodegeneration.

Melatonin: Widely studied for its antioxidant and anti-inflammatory properties, melatonin has recently been shown to reduce microglial activation, modulate the NF-κB pathway, and act as an iron chelator, potentially preventing ferroptosis in neurodegenerative contexts [17]. In an observational clinical study involving patients with intracerebral hemorrhage, melatonin was associated with reduced mortality and better functional outcomes, suggesting neuroprotective benefits in acute injury settings [18].

6.1. Cannabidiol (CBD) and Mitochondrial Mechanisms

Studies using human models and cell cultures demonstrate that CBD modulates microglial activation, reduces oxidative stress, and promotes mitochondrial quality control through mitophagy-related pathways. A recent review by Silva *et al.* (2023) detailed CBD-mediated microglial modulation and induction of mitophagy. In clinical settings, doses ranging from 300 to 800 mg/day have shown improvements in neurocognitive performance and inflammatory markers in patients with

refractory epilepsy, Alzheimer's disease (AD), and Parkinson's disease [19] [20].

6.2. DHEA in Neuroimmune and Mitochondrial Modulation

Dehydroepiandrosterone (DHEA), an endogenous neurosteroid, exhibits potential neuroprotective and anti-inflammatory effects, although clinical evidence remains limited (Table 1). Experimental models show that DHEA activates the TrkA/Akt pathway, inducing the expression of Jmjd3, an enzyme that represses pro-inflammatory gene transcription in microglial cells [21].

Table 1. Main pharmacological and integrative therapies with potential to modulate neuroinflammation, their primary mechanisms, and clinical evidence in humans.

Therapy	Main Mechanism(s)	Clinical Evidence in Humans
Resveratrol, Curcumin, Quercetin, Flavonoids	Antioxidant action (Nrf2, GSH); anti-inflammatory modulation (NF-κB inhibition); activation of SIRT1 pathways	Cognitive improvement; ↓ TNF-α/IL-6; ↓ oxidative stress (RCTs, reviews)
Coenzyme Q10	Optimization of the mitochondrial respiratory chain; ↑ ATP synthesis; membrane antioxidant	Reduction in fatigue and functional improvement in PD and ataxias; ↑ brain ATP levels (RCTs)
Omega-3 Fatty Acids (EPA/DHA)	Anti-inflammatory mediators (resolvins, protectins, maresins); membrane fluidity modulation; ↓ oxidative stress	↓ Inflammatory markers (IL-1β, TNF-α, IL-6); cognitive improvement in AD and MS (RCTs)
Vitamin D	Immunomodulatory; anti-inflammatory; neuroprotective (anti-excitotoxic, antioxidant, synaptic protein regulation); cytokine modulation	Association with lower risk/severity of neurodegeneration; ↓ disease activity in MS; cognitive benefits (RCTs)
N-acetylcysteine (NAC)	Glutathione (GSH) replenishment; Complex I protection; ↓ free mtDNA; anti-inflammatory modulation	↑ Brain GSH (7T MRI); clinical improvement in MS/AD; ↓ inflammatory biomarkers (RCTs, phase II trials)
Alpha-Lipoic Acid (ALA)	Universal antioxidant; regeneration of other antioxidants; NF-κB modulation	Improvement in diabetic neuropathy; potential benefit in MS; limited direct evidence for pure neuroinflammation
Cannabidiol (CBD)	Microglial modulation; ↑ SIRT1; ↑ PINK1/Parkin pathways; ↓ NF-κB; ↓ oxidative stress	Cognitive/symptomatic improvement in epilepsy, AD, PD; ↓ cytokines (RCTs, reviews)
Dehydroepiandrosterone (DHEA)	Regulation of TrkA/Akt → JMJD3 signaling (anti-inflammatory); neuroprotection	Observational: higher DHEAS levels correlated with ↓ IL-6 and better cognitive outcomes; no direct RCTs for neuroinflammation
Transcranial Photobiomodulation (tPBM)	Activation of cytochrome c oxidase; ↑ ATP; ↑ nitric oxide (NO); glial modulation	Cognitive improvement; ↑ brain connectivity; ↓ inflammatory biomarkers (meta-analyses, RCTs)
Probiotics	Modulation of the gut-brain-microbiota axis; alteration of microbial composition; promotion of an anti-inflammatory environment	Improved immune and inflammatory responses in MS (*L. plantarum*, *B. breve*); cognitive improvement in AD (*Lactobacillus*, *Bifidobacterium* spp.)
Mitochondrial Therapy/Gene Editing	Replacement of damaged mitochondria; mtDNA correction (gene editing)	Mitochondrial donation: safe use in human reproduction; gene editing: promising preclinical data

Source: Adapted from Adamu *et al.* (2024); Tastan & Heneka (2024); Kolliker-Frers *et al.* (2021); Rauf *et al.* (2022); Candelario-Jalil *et al.* (2022).

Observational studies in humans have reported that higher circulating levels of DHEAS (DHEA sulfate) are associated with lower IL-6 concentrations and better cognitive outcomes in older adults [22] [23]. However, these findings are essentially correlational, and no randomized clinical trials have yet demonstrated a direct benefit on neuroinflammation or cognitive function. Therefore, the role of DHEA should be viewed as promising but still preliminary, requiring confirmation through controlled clinical studies.

6.3. Transcranial Photobiomodulation (tPBM)

Transcranial photobiomodulation (tPBM) is a noninvasive therapy that employs near-infrared (NIR) light to enhance neuronal metabolism. NIR light is absorbed by mitochondrial cytochrome c oxidase (CCO), leading to increased ATP and nitric oxide (NO) production, which enhances neuronal function, reduces oxidative stress, and modulates glial inflammation [24] [25].

A 2025 meta-analysis involving over 700 patients reported significant cognitive improvements in individuals with mild AD and subjective cognitive decline (SCD) following tPBM. Protocols varied in wavelength (NIR and NIR-II), application mode, and duration, yet consistently showed improvements in memory, attention, and reductions in inflammatory biomarkers [26] [27]. The technique has also shown promise in Parkinson's disease, traumatic brain injury, and depression, with a favorable safety profile [28] [29].

6.4. Probiotics

Probiotics act as modulators of neuroinflammation through the gut-microbiota-brain axis. Studies indicate that manipulating the gut microbiota via probiotic supplementation can improve immune and inflammatory responses in neuroinflammatory conditions such as multiple sclerosis (MS) and Alzheimer's disease (AD).

In multiple sclerosis, strains such as *Lactobacillus plantarum* and *Bifidobacterium breve* have been associated with reduced levels of pro-inflammatory cytokines (e.g., TNF-α and IL-6) and improved intestinal barrier integrity, thereby decreasing the translocation of substances that could exacerbate neuroinflammation [30] [31]. Furthermore, multistrain formulations combining *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, and *Bifidobacterium lactis* have demonstrated reductions in fatigue and improved inflammatory profiles in MS patients [31].

In Alzheimer's disease, multispecies probiotic formulations containing *Lactobacillus* and *Bifidobacterium* species have shown beneficial effects on cognitive performance and reductions in serum inflammatory markers, suggesting modulation of the gut-brain-inflammation axis [32] [33]. Specific strains such as *Lactobacillus helveticus* and *Bifidobacterium longum* have demonstrated potential in improving cognitive function and inflammatory biomarkers in patients with mild AD [33]. The beneficial effects of probiotics appear to be linked to their ability to modify gut microbial composition, promoting an anti-inflammatory environ-

ment that may, in turn, attenuate neuroinflammatory responses [30].

6.5. Mitochondrial Therapy and Genetic Mitochondrial Therapy

Mitochondrial therapy aims to address mitochondrial dysfunction through replacement or correction strategies. Mitochondrial donation (Pronuclear Transfer), a reproductive technique, allows for the prevention of maternal mitochondrial disease transmission. In 2025, *LiveScience* reported the birth of eight healthy children in the United Kingdom through this technique, confirming its clinical feasibility [34].

Emerging Mitochondrial Genetic Therapies include RNA targeting and mitochondrial genome editing (CRISPR-like technologies) for precise correction of mtDNA mutations. Although still in preclinical stages, these methods hold great promise for future therapeutic applications.

7. Conclusion and Future Perspectives

Neuroinflammation represents a central process in various neurological, psychiatric, and degenerative conditions, reflecting a persistent immune response within the central nervous system. Its clinical recognition is essential, as it is associated with cognitive, emotional, and functional symptoms that significantly impact patient quality of life.

Increased intestinal permeability emerges as a key pathophysiological link between peripheral inflammation and neuroinflammation. Neurodegenerative and psychiatric disorders share mechanisms driven by bacterial translocation and immune activation. Dietary interventions, probiotics, prebiotics, and pharmacological modulators represent promising strategies; however, they still require further clinical validation.

Future advances will depend on identifying reliable biomarkers and conducting robust clinical trials to consolidate the relationship between gut health and neurological protection. A continuous, patient-centered care approach may not only mitigate the impact of neuroinflammation but also contribute to healthy aging and the management of chronic brain diseases.

8. Limitations

As this is a narrative review, the study is subject to selection bias and methodological limitations inherent to this format. The literature search did not follow a predefined systematic protocol, which may have led to the unintentional exclusion of relevant studies or the overrepresentation of certain findings. Therefore, the conclusions presented here should be interpreted with caution, emphasizing the need for future controlled clinical trials and systematic reviews to strengthen the evidence base and better inform clinical practice.

Conflicts of Interest

None declared.

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