J. Pharm Pract Comm Med, 2025; 11(3):22-26.
www.jppcm.org

Review Article

Neuroinflammation in Neurology and Psychiatric Disorders, Mechanisms, Challenges and Emerging Therapeutic Strategies

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ABSTRACT

Neuroinflammation has emerged as a pivotal process underlying a wide spectrum of neurological and psychiatric disorders. Unlike peripheral immune responses, inflammation within the central nervous system involves a tightly regulated interplay between resident immune cells, such as microglia and astrocytes, and molecular signaling pathways uniquely adapted to the brain's microenvironment. This paper explores the multifaceted mechanisms that initiate and sustain neuroinflammation, highlighting key cellular and molecular mediators including cytokines, chemokines, and the complement system. Disruption of the Blood–Brain Barrier, immune cell infiltration, and chronic microglial activation are examined as central contributors to disease progression. Current therapeutic approaches, including non-steroidal anti-inflammatory drugs, corticosteroids, and disease-modifying agents for multiple sclerosis, are critically reviewed in the context of their effectiveness and limitations. The paper further discusses emerging therapies aimed at microglial modulation, inflammasome inhibition, and oxidative stress reduction. Emerging approaches such as stem cell therapies, RNA-based medications, and targeted drug delivery systems represent promising directions for future treatment. Refinements in our understanding of immune mechanisms within the central nervous system are paving the way to more targeted and effective approaches for treating neuroinflammatory conditions.

Keywords: Neuroinflammation, Central nervous system, Microglia, Blood–brain barrier, Cytokines, Neurodegenerative disorders, Psychiatric Illness, Anti-inflammatory Therapy, Microglial Modulation, Emerging Therapeutics.

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INTRODUCTION

Neuro inflammation is a complex and multidimensional immune response that occurs within the central nervous system triggered by various factors such as trauma, infection, ischemia, and neurodegenerative changes (Chitnis and Weiner, 2017). Unlike the broad and systemic nature of peripheral inflammation, neuro inflammation is precisely regulated within the highly specialized environment of the brain and spinal cord. It involves distinct immune cells and signaling mechanisms that aim to preserve a delicate balance between neuroprotection and potential tissue damage (Heneka *et al*., 2015). In recent years, neuro inflammation has increasingly been recognized not merely as a by-product of neural injury, but as a central contributor to the underlying mechanisms of disease. Growing evidence links sustained neuroinflammatory processes to the progression of several major central nervous system disorders, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis (Heneka *et al*., 2015). Moreover, a growing body of research highlights the role of neuroinflammatory processes in psychiatric conditions such as major depressive disorder and schizophrenia. In these disorders, inflammatory cytokines have been found to affect both neurotransmission and neuroplasticity (Ising and Heneka, 2018).

Microglia, the central nervous system's innate immune cells, play a pivotal role in initiating neuro inflammation. In response to infection or cellular damage, these cells become activated and, together with reactive astrocytes, secrete a diverse range of inflammatory and regulatory molecules that can affect both neurone viability and synaptic activity (Jaturapatporn, Isaac, McCleery, and Tabet, 2012). When the integrity of the Blood–Brain Barrier (BBB) is disrupted, the inflammatory response intensifies, as immune cells from the periphery-such as monocytes and T lymphocytes-gain access to the brain, further contributing to inflammation and potential neuronal harm (Jaturapatporn, Isaac, McCleery, and Tabet, 2012).

OPEN ACCESS

Manuscript TECHNOMEDIA

DOI: 10.5530/jppcm.20250047

Publishing Partner : Manuscript Technomedia. [www.mstechnomedia.com]

Although significant progress has been made in understanding peripheral inflammation, translating these insights into effective treatments for Central Nervous System (CNS) disorders remains challenging. Barriers such as limited permeability of the BBB, lack of cellular targeting, and the complex, often dualistic nature of inflammatory mediators have hindered therapeutic success. As a result, current research is shifting toward more precise approaches-focusing on reprogramming microglial activity, suppressing detrimental cytokine responses, and promoting the brain's intrinsic mechanisms for resolving inflammation.

This review explores the fundamental mechanisms driving neuro inflammation, critically assesses existing pharmacological treatments, and highlights emerging experimental strategies currently being studied. By examining the dynamic relationship between immune activity and neural processes, the paper seeks to contribute to the development of more effective and targeted therapies for various neuroinflammatory conditions.

Mechanistic Insights into Neuroinflammation

Immune Cell Dynamics in the CNS

Microglia: The First Responders

Microglia, the brain's resident immune cells, function as vigilant sentinels, constantly monitoring the central nervous system for signs of disruption. When exposed to harmful signals-such as Pathogen-Associated Molecular Patterns or Damage-Associated Molecular Patterns-they rapidly shift in both form and function. Upon activation, microglia adopt polarized states: The M1 phenotype, which promotes inflammation through the release of cytokines like IL-1β, TNF-α, and reactive oxygen species; and the M2 phenotype, which supports anti-inflammatory responses and tissue repair through IL-10 production. While this activation initially serves a protective role, prolonged M1 activity may lead to persistent inflammation and progressive neuronal injury.

Astrocytes and Reactive Gliosis

Astrocytes, once thought to play a purely supportive role, are now known to actively participate in neuro inflammation. Upon CNS injury or immune stimulation, astrocytes undergo reactive astrogliosis, a process marked by hypertrophy and upregulation of glial fibrillary acidic protein. These reactive astrocytes secrete inflammatory mediators, modulate BBB permeability, and influence synaptic remodeling (Ising and Heneka, 2018).

Peripheral Immune Cell Infiltration

Disruption of the blood–brain barrier permits the infiltration of circulating immune cells-such as monocytes, neutrophils, and T lymphocytes-into the central nervous system. Once inside, these cells amplify the inflammatory response by releasing cytokines, generating oxidative stress, and initiating antibody-driven cytotoxic mechanisms. Such immune cell infiltration is a defining feature of neurological disorders like multiple sclerosis and various CNS infections.

Molecular Signaling and Inflammatory Mediators

Cytokines and Chemokines

Pro inflammatory cytokines such as IL-1β, IL-6, and TNF-α play a central role in initiating neuroinflammatory responses by triggering transcription factors like NF-κB, which further propagate the inflammatory signaling cascade. Additionally, chemokines including CCL2 and CXCL10 promote the recruitment of immune cells into affected regions of the central nervous system, thereby sustaining and intensifying local inflammation (Kumar, Lim, More, Kim, and Kim, 2020).

Complement System Activation

Complement proteins, which are normally involved in immune defense, also play a role in shaping neural circuits by pruning synapses. However, in disease states, their abnormal activation can lead to harmful effects, including the recruitment of immune cells and direct damage to neurones. This dysregulation has been strongly associated with conditions like Alzheimer's disease and multiple sclerosis, where it contributes to both neuronal loss and increased glial activity (Kwon and Koh, 2020).

Pattern Recognition Receptors and Inflammasomes

Toll-like receptors and Nucleotide-Binding Oligomerization Domain-like Receptors (NLRs) serve as key sensors of infectious agents and cellular damage within the central nervous system. Among them, the NLRP3 inflammasome plays a pivotal role by processing proinflammatory cytokines-specifically pro-IL-1β and pro-IL-18-into their active forms, thereby sustaining the inflammatory response. Persistent activation of this signaling pathway has been associated with the progression of neurodegenerative diseases and mood-related disorders (Ransohoff, 2016).

Blood–Brain Barrier Dysfunction

The BBB is a highly selective, semipermeable boundary formed by tightly connected endothelial cells, with structural and functional support from astrocytic end-feet and pericytes. This complex architecture ensures that the CNS remains protected from potentially harmful substances circulating in the blood. However, during neuroinflammatory states, pro-inflammatory cytokines such as TNF-α and IL-6 can compromise the integrity of the BBB by disrupting the tight junctions between endothelial cells. As a result, the barrier becomes more permeable, allowing peripheral immune cells and neurotoxic molecules to enter the brain. This infiltration not only escalates the local inflammatory response but also contributes to oxidative stress and neuronal damage, creating a vicious cycle that can drive the progression of various neurological disorders (Jaturapatporn, Isaac, McCleery, and Tabet, 2012).

Neuroinflammation in Disease Contexts

Alzheimer's Disease

In the context of Alzheimer's disease, microglia are frequently observed surrounding amyloid-β plaques and neurofibrillary tangles composed of hyper phosphorylated tau. In the early stages, this clustering reflects the microglial attempt to clear these pathological proteins through phagocytosis. However, as the disease progresses, persistent exposure to amyloid-β and tau aggregates leads to prolonged microglial activation. This chronic activation results in the sustained release of pro-inflammatory cytokines and the generation of reactive oxygen species, which in turn exacerbate neuronal damage and contribute to synaptic dysfunction. Over time, this shift from protective to harmful activity plays a key role in the progression of neurodegeneration and cognitive decline seen in Alzheimer's pathology (Ising and Heneka, 2018).

Parkinson's Disease

Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic autoimmune disorder marked by aberrant T-cell responses directed against the myelin sheath that insulates nerve fibers within the CNS. Autoreactive $CD4^+$ and $CD8^+$ T lymphocytes infiltrate the CNS by crossing the compromised blood–brain barrier, where they recognize myelin antigens as foreign and initiate an inflammatory attack. These T cells, in coordination with activated microglia, release a cascade of proinflammatory cytokines such as IFN-γ, TNF-α, and IL-17, which not only damage myelin-producing oligodendrocytes but also create a toxic environment for neurones. The resulting demyelination impairs the efficient transmission of electrical impulses along axons, leading to a wide range of neurological symptoms. Over time, repeated inflammatory episodes contribute to irreversible axonal injury and neurodegeneration, driving the progression of disability in MS patients (Serhan and Levy, 2018).

Traumatic Brain Injury and Stroke

Acute injuries to the central nervous system, such as traumatic brain injury or stroke, trigger an immediate inflammatory response characterized by the swift activation of microglia and the infiltration of peripheral immune cells. Initially, this response plays a beneficial role by facilitating the clearance of cellular debris and promoting tissue repair. However, if the inflammatory process becomes prolonged or dysregulated, it can lead to secondary damage. Chronic release of proinflammatory cytokines, reactive oxygen species, and other neurotoxic factors may exacerbate neuronal loss, impair synaptic function, and hinder recovery. This shift from protective to pathological inflammation is a critical factor in the worsening of outcomes following acute CNS injury (Kwon and Koh, 2020).

Psychiatric Disorders

Elevated levels of inflammatory cytokines have been documented in depression, bipolar disorder, and schizophrenia. These cytokines can alter neurotransmitter metabolism, synaptic plasticity, and stress responses, linking neuroinflammation to psychiatric symptoms (Serhan and Levy, 2018).

Pharmacological Approaches in Neuro-inflammation

Current therapeutic strategies targeting neuroinflammation focus on suppressing inflammatory cascades, preserving BBB integrity, and mitigating neuronal damage. However, many conventional treatments demonstrate limited efficacy in CNS disorders due to poor BBB permeability and a lack of cellular specificity.

Corticosteroids remain a mainstay in the management of acute neuroinflammatory episodes. High-dose intravenous methylprednisolone is commonly used during multiple sclerosis relapses, while dexamethasone is frequently administered to manage cerebral edema in the context of CNS infections, tumors, and trauma. These agents act by suppressing proinflammatory gene transcription via glucocorticoid receptor pathways. Despite their potent effects, long-term corticosteroid use is limited by systemic side effects and potential neurotoxicity.

In MS, disease-modifying therapies such as interferon-β and glatiramer acetate are widely prescribed to modulate T-cell responses and reduce relapse rates. Newer agents like fingolimod and ocrelizumab offer enhanced efficacy by targeting lymphocyte trafficking and B-cell depletion, respectively (Tay, Savage, Hui, Bisht, and Tremblay, 2017).

Therapy type	Example drug	Mechanism	Limitation
Corticosteroids	Dexamethasone, Methylprednisolone.	Broad immune Suppression.	Long-term toxicity.
NSAIDs	Ibuprofen.	COX inhibition.	Poor BBB penetration.
Disease-modifying Drugs	Interferon-β, Fingolimod.	T/B cell modulation.	Limited efficiency in late stages.
Emerging therapies	CSF1R inhibitors, NLRP3 blockers.	Microglialreprogramming, inflammasomeinhibition.	Still experimental, lacks clinicalValidation.

Abbreviations: BBB-Blood–Brain Barrier.

The non-steroidal anti-inflammatory drugs and tumor necrosis factor-alpha (TNF-α) inhibitors which have already demonstrated their potential in preclinical models of neurodegenerative diseases-by often reducing inflammation and also by slowing down the disease progression-their full effectiveness in clinical settings till now has been far less consistent. In patients who have already been established with CNS disorders, such as Alzheimer's disease and Parkinson's disease, these agents have till now yielded mixed results, with showing very limited therapeutic benefit and showing inconsistent outcomes across trials. To improve the outcomes few factors such as timing of intervention, disease stage, blood–brain barrier permeability, and individual immune profiles might contribute to lack of efficacy, and highlight need for more potent compounds needed for pharmacotherapy.

Emerging Therapeutic Strategies

There are new strategies which are being developed for the treatment of neuroinflammatory disorders. The major focus is on NLRP3 inflammasome, which drives the release of IL-1β and IL-18 during chronic CNS inflammation. Targeting NLRP3 or its upstream regulators, such as the P2X7 receptor, which has shown good results in reducing neurotoxicity in preclinical results.

Others such as Modulating microglial activity has also gained attention as a therapeutic strategy. Compounds such as CSF1R inhibitors (e.g., PLX3397) shows the ability to deplete or alter the behavior of activated microglia, helping to reduce neuroinflammatory responses (Ransohoff, 2016).

Another new strategy agent targets Nrf_2 pathway, which plays a key role in regulating antioxidant defenses. Drugs like dimethyl fumarate, which is already being used in multiple sclerosis, work by activating Nrf_2 and lowers oxidative stress.

These therapies are still in the early phase of their trial and need far more precious and funded research for profound results. So that they could be used commercially.

DISCUSSION

Neuro inflammation is increasingly involved in the acute and chronic peripheral and central inflammation disorders of which various neurological and psychiatric conditions are a part of. Although it begins as a protective response to injury or infection, a long activation of this mechanism can lead to harm more than good-causing further damage to neurones, disrupting synaptic function, and ultimately worsening disease outcomes.

Its dual role as a protective mechanism as well as destructive mechanism makes it a complex area of study. Existing treatments, such as corticosteroids and disease-modifying drugs used in multiple sclerosis, may offer short-term benefits but fall short in addressing the ongoing immune dysregulation characteristic of progressive neurodegenerative diseases. The challenge would be to cross the blood brain barrier of not.

Recent progress in understanding microglial dynamics, inflammasome signaling, and oxidative stress pathways has paved the way for more targeted therapeutic approaches. Instead of broadly suppressing the immune system, newer strategies aim to fine-tune neuroimmune interactions-an approach that holds considerable promise.

CONCLUSION

Overall, despite the significant advances in neuroinflammation it still remains a long area of research but if the complications and solved it might help a lot a disorders with much less side effect prone drugs.

Neuro inflammation is increasingly involved in the acute and chronic peripheral and central inflammation disorders of which various neurological and psychiatric conditions are a part of. Traditional anti-inflammatory treatments which have shown limited success in the CNS, largely due to obstacles such as inadequate blood–brain barrier penetration and broad immunosuppressive effects. However, this neuroinflammation treatment can be helpful in solving much complex disorders which much simpler drugs.

ABBREVIATIONS

CNS: Central Nervous System; **BBB:** Blood–Brain Barrier; **PAMPs:** Pathogen-Associated Molecular Patterns; **DAMPs:** Damage-Associated Molecular Patterns; **IL-1β:** Interleukin-1 Beta; **TNF-α:** Tumor Necrosis Factor Alpha; **IL-10:** Interleukin-10; **IL-6:** Interleukin-6; **CCL2:** C-C Motif Chemokine Ligand 2; **CXCL10:** C-X-C Motif Chemokine Ligand 10; **NF-κB:** Nuclear Factor Kappa B; **NLRs:** Nucleotide-Binding Oligomerization Domain-like Receptors; **NLRP3:** NLR Family Pyrin Domain Containing 3; **MS:** Multiple Sclerosis; **CD4+:** Cluster of Differentiation 4 Positive T Lymphocytes; **CD8+:** Cluster of Differentiation 8 Positive T Lymphocytes; **IFN-γ:** Interferon Gamma; **IL-17:** Interleukin-17; **NSAIDs:** Non-Steroidal Anti-Inflammatory Drugs; **CSF1R:** Colony Stimulating Factor 1 Receptor; **P2X7:** Purinergic Receptor P2X7; **Nrf2:** Nuclear Factor Erythroid 2–Related Factor 2; **IL-18:** Interleukin-18; **ROS:** Reactive Oxygen Species; **COX:** Cyclooxygenase; **TNF inhibitors:** Tumor Necrosis Factor Inhibitors.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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Cite this article: Sharma S, Harshita. Neuroinflammation in Neurology and Psychiatric Disorders, Mechanisms, Challenges and Emerging Therapeutic Strategies. J Pharm Pract Comm Med. 2025;11(3):22-6.