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Targeting Neuroinflammation in Bipolar Disorder: A New Era in Treatment Approaches

Smith Woolsey*

Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA

Introduction

Bipolar Disorder (BD) is a chronic, recurrent mood disorder characterized by alternating episodes of mania/hypomania and depression. Affecting approximately 1–3% of the global population, BD imposes a significant burden on individuals, families and healthcare systems due to its high rates of relapse, comorbidity and suicide. Despite substantial advances in psychopharmacology, a large subset of patients experiences partial or non-response to traditional mood stabilizers such as lithium, valproate, or atypical antipsychotics. This therapeutic gap has spurred a search for novel targets and pathophysiological insights, with growing attention directed toward the role of neuroinflammation in the etiology and progression of BD. Emerging evidence suggests that inflammatory processes-both systemic and central-contribute to the pathophysiology of bipolar disorder. Elevated levels of pro-inflammatory cytokines, microglial activation, oxidative stress and Blood-Brain Barrier (BBB) dysfunction are consistently observed in patients with BD, particularly during mood episodes. These findings have prompted the development of anti-inflammatory and immunomodulatory interventions as potential therapeutic strategies [1].

Description

Neuroinflammation refers to the activation of the brain's innate immune system, primarily driven by microglia, astrocytes and endothelial cells in response to injury, infection, or stress. In bipolar disorder, this immune activation appears chronic, low-grade and widespread, involving both peripheral immune signaling and central nervous system responses. Numerous studies have demonstrated elevated concentrations of pro-inflammatory cytokines in BD patients, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β) and C-reactive Protein (CRP). These markers are particularly increased during manic and depressive episodes and tend to normalize during euthymia, suggesting a state-dependent role of inflammation. Microglia is the primary immune effector cells in the brain. In BD, microglial activation contributes to neurotoxicity via the release of Reactive Oxygen Species (ROS), nitric oxide and inflammatory mediators. Postmortem and neuroimaging studies reveal increased microglial density and activity in key mood-related brain regions such as the anterior cingulate cortex and hippocampus [2].

Neuroinflammation and oxidative stress are closely intertwined. Patients with BD exhibit increased lipid peroxidation, protein oxidation and mitochondrial DNA damage, indicative of heightened oxidative stress. Mitochondrial dysfunction contributes to impaired neuronal energy metabolism, apoptosis and neurotransmitter imbalance. Compromised BBB integrity allows peripheral immune cells and cytokines to access the central nervous system, further propagating neuroinflammatory cascades. Studies show altered tight junction protein expression and increased permeability in BD, particularly during acute mood episodes. Pro-inflammatory cytokines can activate the enzyme Indoleamine 2,3-Dioxygenase (IDO), which diverts tryptophan metabolism toward the kynurenine pathway, producing neurotoxic metabolites such as quinolinic acid. This pathway is implicated in glutamatergic excitotoxicity and mood regulation. [3].

Identifying reliable biomarkers of inflammation in BD could facilitate precision medicine approaches. Peripheral blood markers like CRP, IL-6 and TNF-α show potential, although variability across studies remains a challenge. Neuroimaging modalities such as Positron Emission Tomography (PET) using radioligands targeting the Translocator Protein (TSPO) on activated microglia have provided insight into central inflammation. Additionally, inflammatory signatures may help predict treatment response. For example, elevated baseline CRP has been associated with poorer outcomes to SSRIs but better response to anti-inflammatory agents in depressive disorders. This suggests a potential for inflammation-guided treatment stratification in BD as well. The recognition of inflammation's role in BD has catalyzed research into anti-inflammatory and immunomodulatory treatments. These agents are being explored as adjunctive or stand-alone therapies, particularly in treatment-resistant cases [4].

Adjunctive use of NSAIDs such as celecoxib, a COX-2 inhibitor, has shown promise in reducing depressive symptoms in BD. A Randomized Controlled Trial (RCT) reported that celecoxib added to valproate significantly improved depressive symptoms and inflammatory markers. Minocycline, a tetracycline antibiotic with anti-inflammatory properties, inhibits microglial activation and reduces oxidative stress. Small trials have shown positive effects on depressive symptoms in BD when used adjunctively. Its ability to cross the BBB and modulate central inflammation makes it a promising candidate. Omega-3 PUFAs, particularly Eicosapentaenoic Acid (EPA), exert anti-inflammatory effects by inhibiting pro-inflammatory eicosanoid synthesis. Meta-analyses have found modest antidepressant effects of omega-3 supplementation in BD, especially in depressive episodes. NAC replenishes intracellular glutathione and acts as a free radical scavenger. Several RCTs in BD have demonstrated significant improvement in depressive symptoms and functioning with NAC augmentation. Its antioxidant and anti-inflammatory mechanisms underlie its therapeutic efficacy. Biologic agents targeting specific cytokines, such as infliximab (TNF-α inhibitor) and tocilizumab (IL-6 receptor antagonist), are under investigation. Preliminary findings suggest that patients with elevated inflammatory markers may benefit most. Safety concerns and high costs, however, limit widespread use [5].

Conclusion

The recognition of neuroinflammation as a central contributor to bipolar disorder marks a paradigm shift in understanding and treating this complex condition. Inflammatory processes involving cytokine dysregulation, microglial activation, oxidative stress and BBB disruption are implicated in the pathogenesis and progression of BD. Targeting these pathways with anti-inflammatory and immunomodulatory therapies opens new avenues for treatment, particularly in patients who do not respond to conventional mood stabilizers. While challenges persist-such as biomarker variability, safety concerns and limited large-scale evidence-the emerging data are compelling. As research advances, integrating neuroinflammatory insights with clinical

***Address for Correspondence:** Smith Woolsey, Department of Neurology, Fujian Medical University, Fuzhou, China, E-mail: woolseysmith@ies.edu*

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practice holds the promise of more effective, personalized and mechanistically driven care for individuals living with bipolar disorder. A new era in treatment-one that recognizes the mind-body-immune connection-is on the horizon.

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Conflict of Interest

None

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