Review Article

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Microglia in Epilepsy: From Circuit Modulators to Therapeutic Targets

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Epilepsy affects over 50 million people worldwide, with one-third resistant to drugs. Once seen as a disorder of neuronal hyperexcitability, it's now recognized as involving complex network dysfunction, where non-neuronal cells, especially microglia, play active roles. Microglia regulate synaptic activity, immune surveillance, and circuit remodeling. They monitor extracellular changes, detect ATP from hyperactive neurons, and respond with process motility. Studies show microglia can both reduce hyperactivity by spine contact and promote excitation by stimulating dendritic filopodia and new synapses. This dual role places microglia at the junction of stability and hyperexcitability. Evidence links maladaptive microglial responses to epileptogenesis, seizures, and network instability, highlighting the importance of glial and immune pathways as therapeutic targets.

Keywords: Microglia–neuron interactions; Epileptogenesis; Neuroinflammation; Glial therapeutic targets

Introduction

Beyond Neurons: Microglia at the Crossroads of Epilepsy and Brain Health

Across the globe, epilepsy poses a significant health challenge, affecting around 1% of the population with serious medical, social, and economic consequences (Fiest et al., 2017; Feigin et al., 2019). Despite the availability of various anti-seizure medications, about 30% of patients don't respond to treatment, highlighting the limitations of current therapies that mainly target neuronal ion channels and neurotransmitter systems. The ongoing burden of drug-resistant epilepsy calls for the scientific community to rethink the cellular and molecular foundations of epileptogenesis and seizure dynamics (Fonseca-Barriendos et al., 2021).

Historically, epilepsy research has focused on neurons, emphasizing abnormal synaptic transmission, channelopathies, and imbalances between excitatory and inhibitory signals. While neurons are clearly key to epileptic discharges, this perspective overlooks the contributions of glial cells and the neuroimmune system.

In recent decades, a paradigm shift has taken place: microglia, astrocytes, and oligodendrocytes are increasingly recognized as active participants in shaping neural circuit excitability (Shen et al., 2022). Microglia, in particular, have emerged as versatile regulators that sense, integrate, and respond to neuronal and environmental signals, positioning them as both protectors and potential instigators of pathological network activity (Wu et al., 2020).

Microglia are unique among CNS cells in their origin, biology, and functions. Derived from yolk sac progenitors that immigrate to and colonize the early developing brain before the blood–brain barrier closes, microglia maintain a self-renewing, long-lived population distinct from peripheral monocytes (Hattori, 2023).

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Once viewed as passive "resting" cells in health, they are now recognized as dynamic surveyors of the parenchyma, constantly extending and retracting processes to monitor their environment. This surveillance is made possible through a rich repertoire of receptors collectively termed the sensome, enabling microglia to detect ATP, chemokines, neurotransmitters, and danger-associated molecular patterns (Hickman and El Khoury, 2019).
Within this sensome, the purinergic receptor P2RY12 plays a central role, mediating rapid responses to ATP/ADP gradients released during neuronal activity or injury. High-resolution in vivo two-photon microscopy studies have revealed striking phenomena: microglial processes rapidly extend toward sites of neuronal hyperactivity, forming contacts that can either stabilize spines or lead to their removal (Eyo et al., 2014). Conversely, microglia have been shown to induce the formation of dendritic filopodia and new excitatory synapses, directly modulating circuit function(Miyamoto et al., 2016). Such bidirectional influences underscore the intimate relationship between microglia and neurons, and suggest that in conditions like epilepsy, where neuronal activity is profoundly altered, microglia may tip the balance toward protection or pathology.

This review aims to (i) provide a detailed overview of microglial biology and their sensome, (ii) highlight experimental evidence of microglial regulation of neuronal activity, (iii) integrate emerging data on microglia's role in epilepsy, and (iv) discuss the potential of targeting non-neuronal elements like microglia, astrocytes, and oligodendrocytes as novel therapeutic avenues for epilepsy

Microglial Biology and the Sensome

Microglia are a unique population of brain-resident immune cells, distinct in both origin and function. Derived from primitive yolk sac–derived myeloid progenitors that colonize the early developing brain before the closure of the blood–brain barrier, these immigrant cells establish a self-renewing, long-lived niche within the central nervous system (CNS) (Alliot et al., 1999). This allows them to establish a long-lasting, self-renewing population within the central nervous system. Unlike peripheral macrophages, microglia maintain independence from circulating monocytes, allowing them to evolve specialized functions tailored to the neural environment. During development, they contribute indispensably to neurogenesis, synaptogenesis, angiogenesis, blood–brain barrier maturation, and myelination, highlighting their central role in shaping the structural and functional foundations of the brain (Pont-Lezica et al., 2011).

In the adult brain, microglia have a ramified shape with fine, moving processes that constantly scan the brain environment. This surveillance activity is driven by their diverse sensory machinery, which includes receptors for various chemicals like ATP, ADP, and neurotransmitters (Hickman and El Khoury, 2019). Among these, the purinergic receptor P2RY12 is especially important. In the adult healthy brain, P2RY12 is only found in microglia and distinguishes them from other brain cells (Walker et al., 2020). It helps microglia respond quickly to chemicals released during brain activity, injury, or seizures. Through P2RY12 signaling, microglia extend processes toward overactive or injured neurons, forming dynamic connections that influence how neurons communicate and the excitability of brain circuits.

Downregulation of P2RY12 marks a key transition from a healthy to an activated state, making it a reliable marker of microglial activation (Walker et al., 2020). This dual role serves both as a cell-specific marker and a functional regulator of microglial activity, putting P2RY12 at the forefront of microglial research. In epilepsy, studies have highlighted its critical role in shaping communication between neurons and microglia, modulating brain hyperactivity, and possibly determining whether microglial responses become helpful or harmful (Gibbs-Shelton et al., 2023). Therefore, P2RY12 exemplifies the broader principle that microglial identity and function are closely linked, positioning these cells as essential guardians of brain development, health, and disease.

Microglia-Neuron Interactions: Bidirectional Regulation

Recent advances in in vivo imaging have transformed our understanding of microglia–neuron interactions, revealing a striking bidirectional role for microglia as both regulators of neuronal hyperactivity and facilitators of excitatory connectivity. A seminal study by Davalos and colleagues (2005) provided the first direct evidence that microglial processes are highly dynamic responders to neuronal stress signals (Davalos et al., 2005). Using laser-induced focal injury in cortical slices and in vivo two-photon microscopy, they showed that the local release of extracellular ATP acts as a potent chemotactic signal, rapidly guiding microglial processes toward the site of damage. This discovery not only established ATP

as a “find-me” cue but also set the stage for later studies investigating microglial surveillance of neuronal activity.

Building on this work, two-photon imaging studies demonstrated that microglia preferentially contact hyperactive neurons and dendritic spines in vivo, where they can either stabilize or selectively eliminate synaptic structures depending on the excitatory load (Eyo et al., 2014; Akiyoshi et al., 2018). These contacts are not merely structural: electrophysiological recordings from mice revealed that microglial engagement reduces excitatory postsynaptic currents and dampens neuronal firing, providing direct evidence that microglia exert inhibitory control over hyperactive circuits. Mechanistically, this pruning process has been traced to the complement pathway, where synapses tagged by complement proteins C1q and C3 are engulfed through microglial complement receptor CR3, a mechanism first clarified in landmark studies from Beth Stevens’s group at Boston Children’s Hospital (Stephan et al., 2012).

Paradoxically, microglia can also promote neuronal activity and circuit remodeling. Miyamoto and colleagues working in Riken’s Brain Science Institute under the guidance of Hiroki Nishiyama, used in vivo imaging of mouse somatosensory cortex to demonstrate that microglial contacts with dendritic shafts induce the rapid formation of filopodia, many of which subsequently develop into stable excitatory synapses (Miyamoto et al., 2016). This effect was shown to depend on microglia-derived brain-derived neurotrophic factor (BDNF) acting on neuronal TrkB receptors, thereby directly enhancing excitatory drive. Together, these findings highlight that microglia are not merely passive guardians against hyperexcitability but also active architects of synaptic connectivity, capable of both dampening pathological activity and fostering the structural plasticity that underpins learning and memory.

Together, these dual functions highlight the exquisite sensitivity of microglia to local neuronal states and their capacity to fine-tune network activity. While essential for normal development and homeostatic plasticity, this plasticity may become maladaptive in pathological contexts such as epilepsy, where persistent neuronal hyperactivity could hijack microglial mechanisms of pruning and connectivity, thereby contributing to disease progression.

Microglia in Epilepsy

Increasingly, epilepsy is being seen not just as a disorder of excessive neuronal activity, but also as a long-term inflammation of the brain. Microglia, the brain’s own immune cells, play a key role in this process. Studies using imaging techniques, measurements of fluid surrounding the brain, and examination of brain tissue after surgery have consistently found that microglia are active in people with epilepsy (Kagitani-Shimono et al., 2023). However, the effects of microglia can be both helpful and harmful, depending on the context.

Microglia switch between states of balance and reactivity in response to various factors. During seizures, microglia respond quickly, extending their reach, sensing ATP through P2Y12 receptors (Eyo et al., 2014). These early responses may help reduce nerve damage by clearing excess glutamate and debris, or calming hyperactive neurons using mechanisms discussed earlier. In contrast, microglia stay activated for a long time in people with epilepsy, driven by ongoing seizures, damage to the blood–brain barrier, and a back-and-forth signaling between neurons and microglia (Zhao et al., 2018). Analysis of brain tissue from individuals with epilepsy and experimental models reveals increased activity in genes related to inflammation and cytokines like IL-1β, TNF-α, and IL-6, with single-cell studies highlighting diverse microglial clusters that either promote inflammation or support repair (Mukhtar, 2020). Cytokines like IL-1β are key players in neuroinflammation, which boost neuronal activity through NMDA receptors, reducing GABAergic inhibition, thanks to p38 MAPK pathways (Khan et al., 2023). Medications such as anakinra, which block IL-1β signaling, show promise in reducing seizure severity (Yamanaka et al., 2021). Meanwhile, TNF-α has mixed effects: soluble forms can trigger excitotoxicity, while membrane-bound variants may aid in remyelination (Michev et al., 2021). IL-6 is associated with neuroinflammation and seizure-related damage, exhibiting both growth-promoting and inflammatory roles (Soltani Khaboushan et al., 2022). Additionally, while the complement system helps clear debris, excessive activation can mistakenly eliminate synapses, particularly inhibitory ones, contributing to hyperexcitability. Notably, elevated complement activation is found in the brain tissue of epilepsy patients.

Microglia engage in dynamic, bidirectional communication with neurons. During neuronal hyperactivity, ATP release activates P2X7 receptors on microglia, leading to IL-1β secretion and enhanced excitability (Engel et al., 2012). Chemokine pathways such as CX3CL1–CX3CR1 and purinergic receptors

like P2RY12 usually help restrain microglial reactivity and guide microglial processes toward hyperactive synapses, contributing to network stabilization. Disruption of these signaling mechanisms worsens seizure susceptibility (Gibbs-Shelton et al., 2023).

Contrary to the earlier view of microglia as primarily detrimental in epilepsy, recent evidence shows they also play beneficial roles. Genetic or pharmacological ablation of microglia, or loss of homeostatic receptors such as CX3CR1 and P2RY12, leads to more severe seizures and delayed recovery. In experimental models, microglia help terminate seizures, limit neuronal injury, and promote functional recovery after hyperexcitability (Gibbs-Shelton et al., 2023). Therapeutically, microglial pathways are attractive targets. Blocking P2X7 reduces seizures in animal models, and IL-1R blockade with anakinra shows benefit in paediatric epilepsies (Engel, 2023). Inhibiting CSF1R has also reduced seizures experimentally, while complement inhibition prevents excessive synapse loss. These strategies highlight microglia as both contributors to pathology and key players in endogenous seizure-limiting mechanisms.

In summary, microglia are not simply drivers of neuroinflammation but act as context-dependent modulators of epilepsy. They prune synapses, release cytokines, and remodel networks, yet also restrain seizures and aid recovery. Their duality presents challenges but also rich opportunities for therapeutic targeting.

Translational and Therapeutic Perspectives on Glial Targets in Epilepsy

1. Non-Neuronal Rationale and Microglial Pathways

Current antiepileptic drugs (AEDs) act largely on neuronal ion channels and neurotransmitter systems, yet nearly one-third of patients remain drug-resistant. This therapeutic ceiling has shifted attention toward non-neuronal targets, with glial cells now recognized as active regulators of excitability and network remodeling. Microglia are particularly central, given their ability to sense neuronal activity, release cytokines, prune synapses, and coordinate with astrocytes and oligodendrocytes.

Among microglial pathways, the P2X7 receptor has been extensively studied: ATP released during hyperactivity activates inflammasome signaling and IL-1β release, driving seizures. P2X7 antagonists such as Brilliant Blue G and JNJ-47965567 reduce seizure burden in rodent models, and P2X7 inhibitors already in trials for psychiatric and inflammatory disorders may be repurposed. Conversely, P2Y12 receptors normally guide microglial processes toward active synapses and stabilize networks; their loss increases seizure severity (Gibbs-Shelton et al., 2023). Other inflammatory targets include IL-1R/TLR signaling, with caspase-1 inhibition (VX-765) and IL-1R antagonism (anakinra) showing preclinical and early clinical benefit, particularly in pediatric epilepsies such as FIRES. The complement cascade represents another axis: aberrant C1q/C3-mediated synaptic pruning weakens inhibitory circuits, while complement inhibition preserves interneuron connectivity and reduces seizures. Finally, CSF1R modulation alters microglial survival; inhibitors like PLX3397 attenuate seizures, but full depletion is detrimental, highlighting the need for temporally restricted or partial modulation. Collectively, these findings illustrate that microglia can be both pathogenic drivers and protective regulators, requiring therapies that suppress harmful signaling while preserving seizure-terminating and reparative roles.

2. Astrocytic and Oligodendrocytic Contributions

Previously thought of as passive support cells, astrocytes and oligodendrocytes are now seen as crucial to epileptic network dynamics. Astrocytes control glutamate clearance, potassium buffering, and gliotransmission; problems with glutamate transporters like EAAT2 increase excitotoxicity, while boosting them with ceftriaxone reduces seizures in models (Zaitsev et al., 2019). Excessive connections between cells through connexin-43 enhance synchronization and seizure spread, whereas blocking connexin limits propagation (Wang et al., 2025). Cytokines from astrocytes (IL-6, TNF-α) also increase gliosis and excitability. Notably, communication with microglia worsens the pathology: microglial TNF-α triggers astrocytic glutamate release, creating a self-reinforcing excitatory loop.

Oligodendrocytes contribute through myelination and metabolic support, processes disrupted in chronic epilepsy. Myelin deficits impair conduction and network stability, while inflammatory cytokines hinder myelin repair. Microglia influence the growth of oligodendrocyte precursors, suggesting that interventions promoting myelin repair could reduce seizure susceptibility and prevent cognitive decline. Together, targets in astrocytes and oligodendrocytes complement microglial interventions by addressing the balance between excitatory and inhibitory signals, synchronization, and long-term circuit integrity.

3. Innovative Personalized Strategies and Challenges

Advances in therapeutic platforms are broadening the scope of interventions that target glial cells. Gene and RNA-based therapies, such as using viruses or nanoparticles to deliver anti-inflammatory cytokines (like IL-10 and TGF-β) or targeting pro-inflammatory mediators with antisense oligonucleotides, allow for precise control of glial activity. Nanomedicine also makes it possible to deliver modulators for CSF1R, P2X7, or IL-1R through the blood–brain barrier with fewer side effects. Non-drug approaches, such as vagus nerve stimulation and transcranial magnetic stimulation, may also reduce seizures by modulating the immune system, although the exact mechanisms involving microglia need more research. Meanwhile, cell-based methods, including transplanting astrocytes and replacing microglial cells, have shown promise in preclinical models by restoring balance and improving the body's ability to cope with stress. To successfully translate these findings into clinical use, we'll need precision medicine approaches. Identifying biomarkers, such as specific gene activity, cytokine levels, and PET scans that show activity in P2X7 or TSPO, may help us pinpoint patients who are most likely to benefit. Timing is also crucial: microglia can help control acute seizures but can worsen pathology in chronic cases, so it's essential to target the right stage of the disease. Ultimately, combining glial-targeted strategies with traditional anti-seizure medications may help overcome drug resistance while minimizing side effects.

Despite promise, glial-targeted therapies face challenges. Microglia are highly plastic, exerting protective and pathological effects depending on context, and are involved in indiscriminate suppression. Rodent–human differences in glial biology complicate translation, while epilepsy's heterogeneity means glial contributions vary across syndromes. Long-term suppression of immune signaling raises concerns about infection, cognition, and plasticity. Careful validation, stratified trials, and long-term monitoring will therefore be critical for safe and effective clinical application.

Discussion

Over the past two decades, microglia have come to be recognized not as static immune sentries but as dynamic regulators of neural circuit function. In the healthy brain, they continuously extend and retract processes in response to environmental cues, integrating signals to facilitate both structural and functional remodeling. In vivo imaging studies have shown that microglia calm hyperactive synapses, prune redundant connections, and support the formation of new excitatory inputs through the release of brain-derived neurotrophic factor.

However, this versatility makes microglia vulnerable in epilepsy. Initially protective, their response becomes harmful under recurrent seizures and blood-brain barrier dysfunction, leading to a reactive state. Reactive microglia secrete pro-inflammatory factors and strip inhibitory synapses, lowering seizure thresholds and perpetuating a cycle of inflammation and hyperexcitability. They operate within a glial consortium, where the dysfunction of astrocytes and oligodendrocytes further destabilizes neural circuits, redefining epilepsy as a disorder of glial-neuronal ecosystems. These insights have significant therapeutic value. Targeting microglial signaling pathways and astrocytic or oligodendrocytic functions offers potential for effective interventions. Advanced platforms, such as nanoparticle delivery and cell therapy, promise innovative ways to modulate glial states, but caution is needed as suppressing microglia could impair their beneficial roles.

Future progress hinges on understanding temporal dynamics in glial functions, recognizing species differences, and identifying biomarkers for monitoring glial states. Importantly, we must appreciate patient heterogeneity, as different epilepsy types may involve distinct glial mechanisms. Ultimately, epilepsy should be viewed not merely as an electrical disorder of neurons but as a disruption of neuroimmune ecosystems. By positioning microglia at the core of these networks, we can move towards true disease modification, enhancing resilience, preserving cognition, and restoring brain health.

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