INOSR APPLIED SCIENCES 13(2):1-6, 2025 ISSN: 2705-165X
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International Network Organization for Scientific Research
https://doi.org/10.59298/INOSRAS/2025/13.2.1600

Beyond Synaptic Plasticity: The Role of Non-Neuronal Cells in Neuromodulation and Neurotoxic Responses

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ABSTRACT

Traditionally, neuromodulation and neurotoxicity have been viewed primarily through a neuronal lens, focusing on synaptic plasticity, neurotransmitters, and circuit-level adaptations. However, recent advances reveal that non-neuronal cells-notably astrocytes, microglia, oligodendrocytes, and brain endothelial cells-play critical roles in modulating neuronal function and mediating toxic responses to environmental and endogenous insults. This review explores the multifaceted contributions of non-neuronal cells in neuromodulation beyond classical synaptic mechanisms, highlighting their roles in neurotransmitter regulation, ion homeostasis, blood-brain barrier integrity, neuroimmune crosstalk, and metabolic coupling. We also examine how dysregulation of these cells contributes to neurotoxicity in conditions such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and toxin-induced encephalopathies. Understanding the integrative functions of non-neuronal elements opens new therapeutic avenues for neurodegenerative and neuropsychiatric disorders.

Keywords: Neuroinflammation, Glial Cells, Blood-Brain Barrier, Neurodegeneration, Neuromodulatory Signaling

INTRODUCTION

The concept of neuromodulation has long been dominated by studies on neurons, particularly the way in which synaptic plasticity and neurotransmitter systems contribute to learning, memory, and adaptive behaviors [1]. However, this neuron-centric model has increasingly come under scrutiny as mounting evidence suggests that non-neuronal cells play indispensable roles in regulating brain function [2]. Cells such as astrocytes, microglia, oligodendrocytes, and endothelial cells contribute actively to synaptic modulation, neuroprotection, and homeostasis [3]. These cells form a dynamic and interconnected neurovascular unit that responds to physiological signals and pathological stimuli in a highly coordinated fashion. The limitations of focusing solely on neuronal mechanisms have become apparent in the face of complex neurological disorders where therapies targeting neurotransmission alone have failed to yield satisfactory outcomes. In diseases such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, and various toxin-induced neurodegenerative conditions, non-neuronal cells are increasingly recognized not as passive bystanders but as pivotal regulators of disease progression and recovery [4]. For instance, the activation of microglia and astrocytes, the loss of oligodendrocyte integrity, and the breakdown of the blood-brain barrier (BBB) are now viewed as central pathological events in many of these disorders [5]. This review aims to highlight the evolving understanding of neuromodulation through the lens of non-neuronal cells. By focusing on the contributions of astrocytes, microglia, and other glial and endothelial cells, we aim to offer a more integrative framework for understanding how the brain maintains functional balance and how its dysregulation leads to neurotoxicity.

Astrocytes in Neuromodulation and Neurotoxicity

Astrocytes are the most abundant glial cells in the central nervous system and serve a wide array of functions beyond their traditional supportive roles. They participate directly in synaptic transmission by releasing gliotransmitters, such as glutamate, ATP, and D-serine, that modulate neuronal excitability and plasticity [6]. Through the formation of the tripartite synapse, astrocytes ensheath synaptic junctions and influence both pre- and post-synaptic elements, thereby shaping information processing in the brain [7]. Additionally, astrocytes are key regulators of

extracellular ion concentrations, particularly potassium, and they play an essential role in neurotransmitter recycling, most notably in the glutamate-glutamine cycle [8].

In terms of neuromodulation, astrocytes contribute to the fine-tuning of synaptic efficacy through calcium-dependent signaling pathways [9]. These calcium waves propagate across astrocytic networks and influence neuronal synchronization and oscillatory activity. Moreover, astrocytes are involved in the regulation of cerebral blood flow by responding to neuronal activity and releasing vasoactive substances that modulate vascular tone [10]. However, under pathological conditions, astrocytes undergo a process known as reactive astrogliosis [11]. This phenotypic transformation can be either protective or harmful, depending on the context and severity of injury. Reactive astrocytes may secrete pro-inflammatory cytokines, promote oxidative stress through the release of reactive oxygen species (ROS), and contribute to excitotoxic damage by impairing glutamate clearance [12]. In neurodegenerative diseases like Alzheimer's and Huntington's disease, astrocytic dysfunction has been linked to synaptic deficits and neuronal death [13]. Furthermore, impaired astrocytic regulation of the BBB can facilitate the infiltration of peripheral immune cells and exacerbate neuroinflammation [14].

Microglial Dynamics in Synaptic Remodeling and Toxic Response

Microglia are the resident immune cells of the central nervous system and play a vital role in both physiological and pathological contexts [15]. In the healthy brain, microglia constantly survey the environment with their motile processes, maintaining homeostasis and engaging in synaptic pruning during development and plasticity [16]. They contribute to synaptic remodeling by engulfing weak or redundant synapses, a function essential for proper neural circuit formation and refinement. Microglial activation is a hallmark of virtually all forms of brain injury and neurodegeneration [17]. Upon encountering pathogens, damaged neurons, or toxic substances, microglia shift from a resting to an activated phenotype [18]. This transition involves morphological changes, upregulation of surface receptors, and the secretion of various signaling molecules including cytokines, chemokines, and ROS [19]. While acute microglial activation can be neuroprotective by clearing debris and pathogens, chronic activation leads to sustained inflammation, synaptic dysfunction, and neuronal damage [20] In neurodegenerative diseases, such as Parkinson's and Alzheimer's, microglia are often found clustered around pathological aggregates like alpha-synuclein and amyloid-beta [17]. These aggregates act as damage-associated molecular patterns (DAMPs), triggering microglial Toll-like receptors and perpetuating a cycle of inflammation and neurotoxicity [21]. Moreover, aging-related changes in microglial function—such as a lowered activation threshold and impaired resolution of inflammation—further exacerbate disease progression [22]. Importantly, microglia interact extensively with astrocytes, endothelial cells, and neurons, forming a complex signaling network [23]. Crosstalk between microglia and astrocytes can amplify inflammatory responses, while interactions with neurons can influence synaptic plasticity and behavior [24]. Therapeutic strategies aimed at modulating microglial activation and polarization states (e.g., M1 pro-inflammatory vs. M2 anti-inflammatory phenotypes) are under investigation as potential treatments for a variety of neurodegenerative and neuroinflammatory conditions [25,26].

Oligodendrocytes and White Matter Modulation

Oligodendrocytes are glial cells primarily recognized for their role in forming myelin sheaths around central nervous system (CNS) axons, which facilitate rapid saltatory conduction of electrical impulses [27]. However, their functions extend far beyond this traditional role. They play a vital role in regulating axonal conduction velocity and ensuring the synchronization of neuronal signaling across distant brain regions [28]. This synchronization is essential for higher cognitive processes such as attention, learning, and memory consolidation. Moreover, oligodendrocytes contribute significantly to metabolic support by transferring lactate and other energy substrates to axons [29]. This metabolic coupling is crucial for maintaining axonal integrity, especially in high-energy-demand regions such as the corpus callosum [30]. Notably, emerging research indicates that oligodendrocyte precursor cells (OPCs), which persist into adulthood, are highly dynamic. They are capable of sensing changes in neuronal activity and responding through proliferation, differentiation, or modulation of myelination patterns [31]. In pathological contexts, oligodendrocyte dysfunction contributes to demyelinating disorders such as multiple sclerosis (MS), where immune-mediated damage leads to myelin loss and axonal degeneration [32]. Even in non-inflammatory conditions such as aging and neurodegeneration, disrupted oligodendrocyte function may impair white matter integrity, contributing to cognitive decline [33]. Additionally, evidence from preclinical models shows that enhancing oligodendrogenesis may promote neural repair and functional recovery, positioning these cells as potential therapeutic targets in a range of CNS disorders [34].

Brain Endothelial Cells and the Neurovascular Interface

Brain endothelial cells form the structural and functional basis of the blood-brain barrier (BBB), a selectively permeable interface that shields the CNS from harmful blood-borne substances [35]. These cells, together with pericytes and astrocytic end-feet, create a tightly regulated microenvironment critical for neuronal function. Through the expression of tight junction proteins and specialized transporters, endothelial cells control the entry and exit of ions, nutrients, and metabolic waste, thus maintaining CNS homeostasis [36]. Under physiological conditions, endothelial cells contribute to neurovascular coupling, wherein local cerebral blood flow is adjusted

according to neuronal activity [37]. They also secrete trophic factors that influence neurogenesis and synaptic remodeling [37]. However, in pathological states such as stroke, traumatic brain injury, and neuroinflammatory diseases, the integrity of the BBB is compromised [38]. Endothelial cell dysfunction permits the extravasation of plasma proteins, immune cells, and neurotoxins into the brain parenchyma, leading to oxidative stress, inflammation, and direct neuronal damage [14]. Importantly, BBB disruption is not merely a consequence but often a precursor to neurodegeneration. For instance, in Alzheimer's disease, vascular dysfunction and reduced endothelial nitric oxide bioavailability have been implicated in amyloid accumulation and impaired cerebral perfusion [39]. Consequently, therapies aimed at preserving or restoring endothelial function are being explored as adjunctive treatments in neurodegenerative diseases and CNS trauma [40].

Intercellular Crosstalk and Integrated Modulation

The CNS is increasingly recognized as a dynamic environment where non-neuronal cells—astrocytes, microglia, oligodendrocytes, and endothelial cells—communicate extensively with neurons and with each other to modulate brain function [41]. These interactions are not passive but involve complex, bidirectional signaling pathways that influence synaptic plasticity, neuroimmune responses, and metabolic equilibrium. Astrocyte-microglia interactions regulate neuroinflammatory states. Astrocytes can release chemokines and cytokines that either prime or suppress microglial activation, depending on the context [42]. Likewise, activated microglia can influence astrocytic responses through the secretion of factors like IL-1β and TNF-α [43]. Astrocytes also engage in metabolic crosstalk with neurons via the astrocyte-neuron lactate shuttle, supplying neurons with lactate as an alternative energy substrate, particularly during periods of high activity [44]. Endothelial-glial communication is another critical axis in neurovascular regulation [45]. Astrocytic end-feet envelop capillaries and sense metabolic needs, relaying signals that influence endothelial permeability and vascular tone [10]. Disruption of any component of this integrated system can result in pathological consequences. For example, aberrant crosstalk between microglia and astrocytes contributes to chronic neurotoxicity in epilepsy, while altered endothelial-glial signaling may exacerbate ischemic injury and blood-brain barrier breakdown [46]. Understanding the nuanced dialogue among these cell types offers new insights into the etiology of neurological diseases and highlights the need for therapeutic strategies that target multicellular networks rather than isolated pathways.

Non-Neuronal Cells in Specific Neurological Disorders

Non-neuronal cells such as astrocytes, microglia, oligodendrocytes, and endothelial cells play pivotal roles in the pathophysiology of various neurological disorders, often acting as mediators of neuroinflammation, excitotoxicity, and vascular dysfunction.

Alzheimer's Disease: In the Alzheimer's brain, astrocytes attempt to clear amyloid-beta (Aβ) through endocytic uptake, but this process becomes overwhelmed, leading to the release of inflammatory mediators [47]. Microglia, while initially protective through Aβ phagocytosis, eventually adopt a chronic pro-inflammatory state that exacerbates neuronal injury [48]. Simultaneously, blood-brain barrier (BBB) breakdown permits toxic plasma components to enter the brain, further driving neurodegeneration [49].

Parkinson's Disease: Microglia are activated by aggregated α-synuclein, a pathological hallmark of Parkinson's disease. This activation leads to the release of pro-inflammatory cytokines and oxidative species [50]. Astrocytic dysfunction, particularly impaired glutamate uptake, contributes to excitotoxicity and dopaminergic neuron death in the substantia nigra [51].

Multiple Sclerosis (MS): In MS, immune cells infiltrate the CNS across a compromised BBB, targeting oligodendrocytes and causing demyelination [52]. This loss of myelin disrupts axonal conduction and initiates a cascade of neurodegeneration. Astrocytes and microglia contribute to lesion formation and scar development [53].

Toxin-Induced Encephalopathies: Exposure to neurotoxic agents like lead, mercury, or industrial solvents disrupts astrocytic energy metabolism and glutamate clearance [54]. Microglia respond by becoming reactive, releasing neurotoxic mediators that amplify brain damage.

Therapeutic Implications

Targeting non-neuronal cells offers promising therapeutic strategies in neurological diseases:

Inhibiting reactive gliosis can limit scarring and restore tissue plasticity [55].

Enhancing astrocytic glutamate clearance may reduce excitotoxic damage in neurodegenerative diseases [56].

Blocking pro-inflammatory microglial signaling can dampen chronic neuroinflammation [57].

Stabilizing the BBB prevents immune cell infiltration and toxic leakage [58].

Promoting oligodendrocyte regeneration holds potential for remyelination and functional recovery in demyelinating disorders like MS. These approaches highlight a paradigm shift from neuron-centric to network-based therapeutic strategies.

CONCLUSION

Neuromodulation is a dynamic, multisystemic process governed by intricate interactions between neuronal and non-neuronal cells. Astrocytes, microglia, oligodendrocytes, and endothelial cells do not merely provide structural

support but actively regulate synaptic activity, neuroinflammation, myelination, and metabolic balance. Their roles become even more pronounced in pathological states, where dysfunction contributes to neurotoxicity and progressive neurodegeneration. A deeper understanding of these glial and vascular elements unveils novel therapeutic targets beyond neurons alone. Future neuroprotective strategies must adopt an integrated approach that considers these non-neuronal contributors to effectively prevent, halt, or reverse the progression of diverse neurological disorders.

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CITE AS: Kungu Erisa (2025). Beyond Synaptic Plasticity: The Role of Non-Neuronal Cells in Neuromodulation and Neurotoxic Responses. INOSR APPLIED SCIENCES 13(2):1-6. https://doi.org/10.59298/INOSRAS/2025/13.2.1600