

Review

Astrocyte-Neuron Interactions in the Neuroinflammatory Cascade of Traumatic Brain Injury

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Abstract

Traumatic brain injury (TBI) is a significant public health concern, leading to substantial morbidity and mortality. While the primary injury is mechanical, the subsequent neuroinflammatory cascade plays a critical role in secondary injury and long-term neurological deficits. Astrocytes, the most abundant glial cells in the brain, play a key role in this cascade, interacting with neurons in a complex interplay that can both protect and exacerbate neuronal damage. This paper aims to provide a comprehensive overview of the intricate interactions between astrocytes and neurons in the neuroinflammatory cascade following TBI. We will discuss the role of astrocytes in initiating and modulating inflammatory responses, their impact on neuronal survival and function, and the potential therapeutic strategies targeting astrocyte-neuron interactions. A systematic review of the relevant literature was



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conducted, focusing on studies investigating the role of astrocytes and their interactions with neurons in the context of TBI. We analyzed studies using various experimental models, including animal models and in vitro cell cultures, as well as clinical studies examining human TBI patients. Astrocytes respond to TBI by undergoing a reactive state characterized by morphological and functional changes. They release various inflammatory mediators, including cytokines, chemokines, and reactive oxygen species, contributing to the inflammatory milieu. While these responses initially aim to protect neurons, prolonged or dysregulated astrocyte activation can exacerbate neuronal damage through glutamate excitotoxicity, oxidative stress, and apoptosis. The intricate interplay between astrocytes and neurons in the neuroinflammatory cascade following TBI is a complex and multifaceted process. Understanding the specific mechanisms underlying these interactions is crucial for developing effective therapeutic strategies. Targeting astrocyte activation, modulating their inflammatory responses, and promoting neuroprotective mechanisms through astrocyte-neuron interactions hold promise for improving outcomes after TBI. Future research should focus on identifying novel therapeutic targets within the astrocyte-neuron communication network to mitigate secondary injury and promote neurofunctional recovery following TBI.

Keywords

Traumatic brain injury (TBI); astrocytes; neuron; neuroinflammation; inflammation; synaptic plasticity; neuroprotection; neurodegeneration

1. Introduction

Traumatic brain injury (TBI) is a significant public health concern, encompassing a broad spectrum of injuries ranging from mild concussions to severe, life-altering events [1]. While initial damage is often caused by physical trauma, the subsequent cascade of events, particularly the neuroinflammatory response, plays a crucial role in determining the long-term consequences of TBI. While the role of neurons in this response is well-established, the complex interplay between neurons and astrocytes, the brain's resident glial cells, remains an area of significant investigation.

TBI is characterized by a complex and multifaceted pathophysiology [1]. The initial impact triggers a cascade of events, including primary injury, characterized by immediate cell death and tissue disruption, and secondary injury, which encompasses a delayed onset of inflammatory and cellular processes [2]. This secondary injury phase, driven by the neuroinflammatory cascade, plays a significant role in exacerbating the initial damage and promoting long-term neurological deficits [2]. Despite the established involvement of both neurons and astrocytes in the neuroinflammatory cascade, several key questions remain unanswered. Specifically, the precise contributions of each cell type, the exact signaling pathways involved in their communication, and the temporal dynamics of their interaction during the inflammatory response remain unclear [3]. While research has shed light on specific aspects of individual cell responses, a comprehensive understanding of the dynamic interplay between neurons and astrocytes, particularly their roles in shaping the inflammatory milieu and influencing subsequent neuronal survival and function, remains elusive [3]. This review addresses these unresolved issues by synthesizing current knowledge on the roles of neurons and

astrocytes in the neuroinflammatory cascade following TBI. We will explore the signaling pathways, molecular mediators, and functional consequences of their interactions, highlighting both protective and detrimental effects. Understanding this interplay is crucial not only for elucidating the mechanisms underlying TBI pathology but also for identifying potential therapeutic targets to mitigate neuroinflammation and improve outcomes for TBI patients.

The lack of effective treatments for TBI highlights the need for further research into the complex mechanisms that drive secondary injury [4]. By providing a comprehensive overview of the dynamic interactions between neurons and astrocytes in the neuroinflammatory response, this review serves as a foundation for future research. It aims to shed light on the crucial role of these cell types in shaping the post-injury environment, ultimately paving the way for the development of innovative therapeutic strategies targeting neuroinflammation to improve treatment outcomes for TBI patients.

2. Astrocyte Activation and Response

Astrocytes, star-shaped glial cells, are widely recognized as the most abundant cell type in the central nervous system (CNS) [5]. Traditionally viewed as passive supporters of neuronal function, recent research has highlighted their active role in synaptic plasticity, neurotransmission, and brain homeostasis [6]. Astrocyte activation, a complex process characterized by morphological and functional changes, is crucial for responding to various CNS insults and maintaining brain health. The following sections discuss the intricate mechanisms underlying astrocyte activation, focusing on the mechanical and biochemical cues that trigger this essential process.

2.1 Mechanical Cues

Mechanical stimuli are increasingly recognized as critical regulators of astrocyte behavior, arising from diverse sources and exerting direct physical forces. While previously the focus was mainly on biochemical signaling, it's becoming clear that these mechanical cues play a vital role in shaping astrocyte morphology, function, and reactivity. Mechanical stimuli play a significant role in shaping astrocyte behavior. Notably, these cues arise from a variety of sources, exerting direct physical forces on astrocytes. These include:

- Blood flow dynamics: Cerebral blood flow fluctuations, especially during neuronal activity, exert mechanical forces on astrocytes. These forces, detected by mechanosensitive ion channels, can trigger calcium signaling and astrocyte activation [7]. However, the precise relationship between flow rate, force magnitude, and specific astrocyte responses (e.g., cytokine release, GFAP upregulation) remains an area of active investigation. Thus, there is a need for future studies to focus on quantifying these forces *in vivo* and correlating them with downstream astrocyte signaling pathways.
- Brain injury: Traumatic brain injury (TBI) or stroke-induced tissue damage generates significant mechanical stress, activating astrocytes via various mechanisms, including cytoskeleton rearrangement and stretch-activated ion channels [8]. Different types of injury, such as compression, stretching, or shear stress from axonal tearing, can elicit distinct astrocyte responses. Compression might primarily activate integrin-mediated signaling, while stretching could preferentially activate stretch-activated ion channels. The specific response will depend on the magnitude, duration, and type of mechanical force applied. Importantly,

the nature of the mechanical injury can dictate whether astrocytes adopt a neuroprotective or neurotoxic phenotype [9]. For example, while moderate compression may induce GFAP expression and scar formation, excessive shear stress can lead to astrocyte necrosis and exacerbate inflammation. Further research is needed to determine the threshold of mechanical stimulation that triggers maladaptive astrocyte responses.

- **Cell-cell interactions:** Astrocyte-astrocyte interactions, as well as interactions with neurons and other glial cells, involve physical contact and mechanical signaling via adhesion molecules and cytoskeletal rearrangements [10]. These interactions can generate tensile or compressive forces, influencing astrocyte morphology and function. For instance, astrocyte processes often wrap around synapses and blood vessels, experiencing constant mechanical strain. This strain can affect the expression of glutamate transporters and the release of gliotransmitters, thereby modulating synaptic transmission and vascular tone. Future studies should investigate how disruption of these mechanical interactions contributes to neurological disorders.

2.2 Biochemical Cues

Diverse biochemical signals contribute to astrocyte activation, leading to complex downstream effects:

- **Inflammatory mediators:** Cytokines, chemokines, and reactive oxygen species (ROS) released during inflammation activate astrocytes through their respective receptors, leading to pro-inflammatory and neuroprotective responses [11].
- **Neurotrophic factors:** Growth factors like BDNF, NGF, and IGF-1 stimulate astrocytic proliferation, differentiation, and neurotrophic support, promoting neuronal survival and recovery [12].
- **Neurotransmitters:** Glutamate, GABA, and ATP can act as neurotransmitters and neuromodulators, activating astrocytes through specific receptors. This leads to changes in astrocyte morphology, calcium signaling, and neurotransmitter uptake [13].
- **Extracellular matrix components:** Components of the ECM, such as laminin, fibronectin, and collagen, can bind to astrocytic receptors, triggering signaling cascades that influence astrocyte morphology and function [14].

2.3 Ethical Clearance Statement

This article does not contain any studies with animals performed by any of the authors. Informed consent was obtained from all authors included in the study.

3. Downstream Effects of Astrocyte Activation

The morphological changes associated with astrocyte activation are dynamic and multifaceted, reflecting their adaptive responses to diverse challenges within the CNS [15, 16]. These changes have significant implications for neuronal function, brain homeostasis, and the overall health of the brain. Astrocytes undergo hypertrophy, increased process branching, and formation of 'reactive gliosis' characterized by thickened processes and increased glial fibrillary acidic protein (GFAP) expression [17]. Notably, reactive Gliosis is a hallmark of astrocyte activation in response to injury,

inflammation, or disease [18]. It involves the formation of a glial scar, a dense, fibrous barrier composed of activated astrocytes and their processes [18]. While this scar serves to isolate the damaged area and prevent further injury, it can also impede neuronal regeneration and contribute to functional deficits.

Astrocytes possess a variety of calcium channels, including voltage-gated calcium channels (VGCCs), ligand-gated channels (e.g., NMDA receptors), and store-operated calcium channels (SOCs) [19]. These channels allow calcium entry from the extracellular space, triggered by various stimuli. Astrocytes also store significant amounts of calcium within intracellular compartments, primarily the endoplasmic reticulum (ER) [20]. This stored calcium can be released through the activation of inositol trisphosphate receptors (IP3Rs) or ryanodine receptors (RyRs), leading to a rapid increase in $[Ca^{2+}]_i$ [21]. Notably, the rise in $[Ca^{2+}]_i$ in one astrocyte can propagate to neighboring cells, forming calcium waves. This intercellular communication mechanism enables coordinated astrocytic activity throughout the brain [22]. This coordinated calcium signaling has far-reaching consequences, influencing neuronal function and synaptic plasticity, partly through the release of gliotransmitters. Astrocytic calcium signaling can lead to the release of gliotransmitters, including glutamate, ATP, and D-serine [23]. These gliotransmitters can modulate neuronal activity by acting on presynaptic terminals, influencing neurotransmitter release, or by directly activating neuronal receptors. Astrocytic calcium can also trigger the uptake of neurotransmitters, particularly glutamate, from the synaptic cleft [24]. This process is crucial for regulating synaptic strength and preventing excitotoxicity. Astrocytic calcium signaling can contribute to synaptic scaling, a process that adjusts synaptic strength in response to the overall level of neuronal activity [25]. This modulation is critical for maintaining neuronal homeostasis and adapting to changing environmental stimuli. Astrocytes play a role in Long-term potentiation, a cellular mechanism thought to be essential for learning and memory formation [26]. Astrocytic calcium signaling can contribute to this process through the release of gliotransmitters and the modulation of synaptic glutamate concentration [27]. Furthermore, activated astrocytic calcium signaling extends beyond the modulation of acute neurotransmission, influencing trophic support and neuronal survival. Activated astrocytic calcium signaling also mediates the release of various neurotrophic factors, including glial cell line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and nerve growth factor (NGF) [28]. These factors promote neuronal survival, growth, and differentiation, assisting in the repair and regeneration process after injury. For instance, the release of GDNF, triggered by calcium influx, can bind to its receptors on neurons, activating downstream signaling pathways that promote cell survival and neurite outgrowth.

Astrocytic calcium signaling is involved in neuroprotective mechanisms, responding to insults like oxidative stress, excitotoxicity, and inflammation [29]. More so, Astrocytes communicate with each other and with neurons through gap junctions. Calcium signaling can modulate the permeability of these junctions, influencing the flow of ions and small molecules, and thus, affecting neuronal activity [30].

Astrocytes interact with various immune cells, including microglia, macrophages, and lymphocytes, to modulate the immune response in the CNS [31]. They produce a wide range of signaling molecules, cytokines, and chemokines that can both promote and suppress inflammation. Astrocytes can release pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6), which activate microglia and macrophages, leading to the production of additional inflammatory mediators [32]. Astrocytes secrete chemokines

that attract neutrophils, monocytes, and lymphocytes to the CNS. For example, CXCL1 and CXCL2 are involved in neutrophil recruitment, while CCL2 and CCL5 attract monocytes and lymphocytes [33]. Astrocytes also produce anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor beta (TGF- β), which inhibit microglial activation and suppress the production of pro-inflammatory mediators [34]. Astrocytes release neuroprotective factors that can mitigate the damaging effects of inflammation. For example, they secrete brain-derived neurotrophic factor (BDNF), which promotes neuronal survival and synaptic plasticity [35]. Importantly, the effects of sex hormones, particularly estrogens, on astrocyte function are well-documented. Estrogens, acting via estrogen receptors expressed on astrocytes, can modulate astrocyte morphology, function, and the release of neurotrophic factors and inflammatory molecules. Under pathological conditions, astrocytes can even synthesize estradiol, acting as a local neuroprotectant [36].

Astrocytes and microglia engage in bidirectional signaling through various receptors and ligands. Activated astrocytes release ATP, which activates microglial P2X7 receptors and promotes microglial activation [37]. Conversely, microglia can release glutamate, which stimulates astrocytic NMDA receptors and induces astrocyte activation. Furthermore, the work by Liddelow et al. [38] demonstrated that activated microglia can cause a specific type of reactive astrocyte, termed A1 astrocytes, through the secretion of IL-1 α , TNF α , and C1q. These A1 astrocytes lose their neurotrophic functions and become neurotoxic, contributing to neuronal death [39]. These interactions form a complex feedback loop that controls the inflammatory response in the CNS. Chronic astrocyte activation can lead to sustained microglial activation and neuroinflammation, which is implicated in neurodegenerative diseases such as Alzheimer's disease and multiple sclerosis [40].

Astrocytes can also modulate the adaptive immune response by interacting with lymphocytes [41]. They express MHC-II molecules, which allow them to present antigens to CD4⁺ T cells. [42] Activated astrocytes release factors that promote T cell activation and differentiation into effector T cells [43]. Additionally, astrocytes can produce chemokines that attract lymphocytes to the CNS [44].

Astrocytes play a crucial role in maintaining the BBB, a protective barrier that restricts the passage of harmful substances from the bloodstream into the brain [45]. Activation can lead to both strengthening and weakening of the BBB, depending on the context. In some cases, activated astrocytes contribute to the formation of a tight BBB, providing a protective barrier against pathogens and toxins. Note that the impact of astrocytes on the BBB after TBI is highly dependent on the injury severity [46], with different types of TBI leading to distinct astrocyte phenotypes and BBB outcomes. However, prolonged activation can also lead to BBB disruption, contributing to neurotoxicity and inflammation.

It is also important to note that the neuroprotective roles of estrogens, including those potentially mediated by astrocytes, in conditions such as traumatic brain injury (TBI) are debated. Sex differences in TBI responses, including the contribution of female sex hormones, are increasingly recognized as essential considerations in preclinical research and treatment development. The specific effects of estrogens in TBI and other neurological conditions require further investigation, as their roles are complex and context-dependent [47].

4. Astrocyte-Neuron Interactions in the Neuroinflammatory Cascade

One crucial aspect of astrocyte-neuron interactions involves gap junction communication, specialized channels that allow direct exchange of small molecules, ions, and signaling messengers between adjacent cells. Gap junctions formed between astrocytes and neurons are particularly relevant in the context of neuroinflammation, a complex process characterized by activation of immune cells and the release of inflammatory mediators, leading to neuronal dysfunction and damage [48].

Astrocytes, through their gap junctional connections with neurons, play a role in the propagation of spreading depolarizations (SDs) [49]. Spreading depolarizations (SDs) are large-scale waves of neuronal and glial depolarization that propagate through the brain tissue. They are characterized by a transient and profound disruption of neuronal activity, accompanied by changes in ion concentrations and blood flow [50]. While SDs can occur physiologically, they are particularly detrimental in pathological conditions such as stroke, trauma, and epilepsy [51]. Astrocytic gap junctions facilitate the synchronization of neuronal activity within interconnected networks during SDs. A recent study has shown that astrocytic gap junctions contribute to the initiation and spread of SDs by coupling neuronal depolarization and facilitating ionic fluxes [52].

Excitotoxicity refers to neuronal cell death caused by excessive stimulation of glutamate receptors, primarily NMDA receptors. This overstimulation triggers a cascade of events, including calcium influx, oxidative stress, and mitochondrial dysfunction, ultimately leading to neuronal cell death, also known as apoptosis. Astrocytes can release glutamate, which may contribute to excitotoxicity under specific conditions. For instance, gap junctions enable the propagation of calcium waves throughout astrocytic networks, and these waves can trigger the release of glutamate. However, astrocytes can also release glutamate via vesicular mechanisms, a process that has been subject to debate. Some studies suggest that astrocytes possess the necessary machinery for vesicular glutamate release, including the vesicular glutamate transporters (VGLUTs) [53]. This release can be triggered by various stimuli, further contributing to excitotoxic neuronal damage. Conversely, other studies have questioned the physiological relevance of vesicular glutamate release by astrocytes, citing low expression levels of VGLUTs or arguing that the observed release is primarily due to other mechanisms [54]. Regardless of the specific mechanism, astrocytic glutamate release plays a role in the neuroinflammatory cascade and its impact on neuronal survival.

Furthermore, in response to the events outlined in Figure 1, reactive astrocytes play a critical role in regulating inflammation following TBI. They can both respond to and produce immunomodulatory molecules, including cytokines and chemokines. Astrocyte pattern recognition receptors, such as toll-like receptors (TLRs) and receptor for advanced glycation end products (RAGE), are stimulated by DAMPs released from damaged cells, leading to activation of nuclear-factor- κ B (NF κ B) signaling. This results in the production of pro-inflammatory cytokines, such as tumor necrosis factor α (TNF α), and inflammatory mediators, including cyclooxygenase-2 and matrix metalloproteinase 9 (MMP-9) [55]. Conversely, astrocytes can also contribute to the clearance of cytotoxic debris, signaling through pattern recognition receptors on phagocytic immune cells in response to DAMPs [55]. The duality of astrocyte function, which promotes both inflammation and its resolution, highlights the complex role of these cells in the neuroinflammatory cascade. Moreover, pattern recognition receptor-mediated NF- κ B signaling in astrocytes also results in cell

swelling, which is implicated in cytotoxic edema —a central pathophysiological mechanism underlying the harmful increase in intracranial pressure following TBI [55].

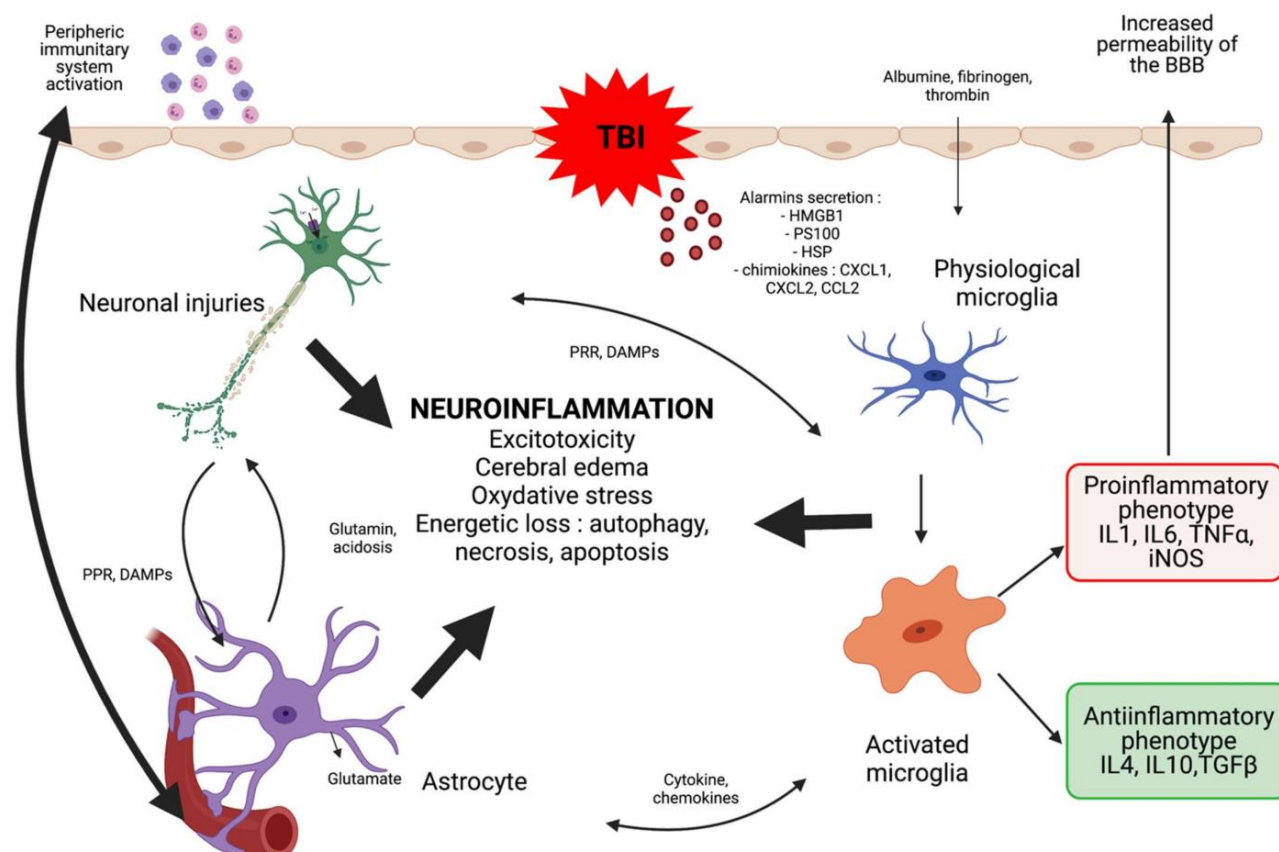


Figure 1 depicts traumatic brain injury (TBI), a cascade of events unfolds leading to post-traumatic neuroinflammation. It illustrates this process, beginning with the rupture of the blood-brain barrier (BBB) and the subsequent release of alarmines, also known as Damage-Associated Molecular Patterns (DAMPs), from injured cells. This release, coupled with the production of cytokines, initiates the activation of endothelial cells, astrocytes, and microglia. Microglia, in particular, undergo a conformational change, adopting an amoeboid shape and migrating towards the site of injury. This response is both localized and generalized, involving the secondary recruitment of the peripheral immune system.

4.1 Astrocyte-Neuron Glutamate Exchange

Astrocytes express high levels of glutamate transporters, particularly the glutamate transporter 1 (GLT-1), which is responsible for the majority of glutamate uptake from the synaptic cleft [56]. GLT-1 is crucial for maintaining low extracellular glutamate levels, which are essential for preventing neuronal excitotoxicity [56]. Glutamate binds to GLT-1 transporters on the astrocyte membrane and is transported into the astrocyte cytoplasm against its concentration gradient using energy derived from sodium and potassium ion exchange [57]. Once inside the astrocyte, glutamate is converted to glutamine by the enzyme glutamine synthetase. Glutamine is released from astrocytes into the extracellular space, where it can be taken up by neurons [57].

Traumatic brain injury (TBI) is a significant cause of neurological disability and can disrupt the astrocyte-neuron glutamate exchange. Following TBI, elevated extracellular glutamate levels are observed [58]. Injured neurons release large amounts of glutamate as a result of membrane damage and ion channel dysfunction. GLT-1 transporters are downregulated and their function is impaired after TBI, resulting in reduced glutamate clearance by astrocytes [59]. Astrocyte death or dysfunction can further contribute to impaired glutamate clearance. This impaired glutamate clearance following TBI can lead to excitotoxicity, which results in neuronal damage and death [59]. Excitotoxicity occurs when extracellular glutamate levels exceed the capacity of synaptic receptors and glutamate transporters, resulting in the sustained activation of glutamate receptors, particularly the NMDA receptor [60]. This excessive activation results in increased intracellular calcium levels, which can trigger a cascade of events including oxidative stress, mitochondrial dysfunction, and ultimately neuronal cell death.

4.2 Astrocyte-Neuron Purinergic Signaling

Purinergic signaling is an essential mechanism for intercellular communication in the CNS, including between astrocytes and neurons. Purinergic receptors are activated by extracellular nucleotides and nucleosides, such as adenosine triphosphate (ATP) and adenosine [61]. Astrocytes release ATP and adenosine under both physiological and pathological conditions [62]. ATP release can occur through various mechanisms, including vesicular exocytosis, hemichannel opening, and gap junction hemichannels [63]. Adenosine is primarily generated from ATP by the enzyme ecto-5'-nucleotidase (CD73). Neurons express both P2X and P2Y purinergic receptors [63, 64]. P2X receptors are ionotropic receptors that allow the passage of cations upon ATP binding, resulting in membrane depolarization and neurotransmitter release [65]. P2Y receptors are metabotropic receptors that activate G proteins upon binding of ATP or adenosine, leading to downstream signaling cascades [66]. The effects of astrocyte-neuron purinergic signaling on neurons depend on the specific purinergic receptors activated, the extracellular ATP and adenosine concentrations, and the cellular context [67]. Activation of P2X7 receptors on neurons can trigger protective mechanisms, such as the release of neurotrophic factors and the inhibition of apoptosis [68]. Activation of P2Y1 receptors on neurons can enhance neuron survival and reduce inflammation [69]. Adenosine signaling via A1 receptors can reduce neuronal hyperexcitability and protect against excitotoxicity [70]. Excessive activation of P2X7 receptors on neurons can lead to excitotoxicity and cell death [71]. Sustained activation of P2Y2 receptors on neurons can promote inflammation and neuronal damage. High levels of extracellular adenosine can lead to the activation of A2A receptors, which can suppress neuronal activity and impair neurotransmission.

Importantly, this purinergic communication is bidirectional. Neurons also release ATP and adenosine, influencing astrocyte activity through astrocyte purinergic receptors. Astrocytes express a variety of purinergic receptors, including P2X and P2Y subtypes [67, 68]. Activation of these receptors on astrocytes can lead to changes in intracellular calcium levels, release of gliotransmitters, and modulation of astrocyte morphology and function. For example, neuronal release of ATP can activate P2Y1 receptors on astrocytes, triggering calcium waves that propagate through the astrocyte network [72]. This, in turn, can influence neuronal activity through the action of astrocyte-derived factors. Furthermore, activation of P2X receptors on astrocytes can modulate the release of glutamate and other gliotransmitters, directly impacting synaptic transmission [73].

Therefore, the interplay between neuronal and astrocyte purinergic signaling is crucial for maintaining proper CNS function and is often disrupted in disease.

4.3 Astrocyte-Mediated Neuroprotection

Astrocytes produce several neurotrophic factors that promote the survival, growth, and differentiation of neurons. These factors include brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and insulin-like growth factor-1 (IGF-1). BDNF is a particularly important neurotrophic factor, as it has been shown to promote the survival of new neurons in the adult brain [74]. Astrocytes can increase the production of BDNF in response to brain injury, which may help to protect neurons from damage. Following brain injury, astrocytes undergo a process of reactive astrogliosis, in which they become enlarged and form a glial scar [75]. The glial scar acts as a physical barrier, preventing further damage to the brain tissue. It also helps to regulate inflammation and repair [76]. The glial scar is not always beneficial. In some cases, it can inhibit the regeneration of damaged neurons [77]. Astrocytes can also modulate synaptic plasticity. This modulation is mediated by the release of neurotransmitters and neuromodulators from astrocytes [78]. Astrocytes can release glutamate, which is an excitatory neurotransmitter, and GABA, which is an inhibitory neurotransmitter [79]. The release of these neurotransmitters can have a direct effect on the strength of synapses. Astrocytes can also release ATP, which is a neuromodulator that can affect the activity of neurons and synapses [78].

4.4 Astrocyte-Mediated Neurotoxicity

Astrocytes are immune-competent cells that can produce and release a wide range of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6) [80, 81]. These cytokines are essential for initiating and resolving inflammatory responses. However, excessive or prolonged release of pro-inflammatory cytokines can lead to neurotoxicity [79]. In neurodegenerative diseases such as Alzheimer's disease and multiple sclerosis, activated astrocytes release high levels of pro-inflammatory cytokines, which can directly damage neurons and disrupt synaptic function [82]. These cytokines can also recruit and activate other inflammatory cells, further amplifying the inflammatory response and contributing to neuronal loss.

Glutamate is the primary excitatory neurotransmitter in the CNS. Under normal conditions, astrocytes help maintain glutamate homeostasis by rapidly clearing glutamate from the synaptic cleft through specific transporters [83]. However, in pathological conditions, astrocytic glutamate clearance can be impaired, leading to excitotoxicity. Excessive glutamate accumulation in the synaptic cleft overstimulates NMDA and AMPA-type glutamate receptors on neurons, causing an influx of calcium ions [84]. This calcium overload can activate various intracellular signaling pathways, ultimately leading to neuronal death. Dysregulated glutamate clearance by astrocytes has been implicated in several neurological disorders, including stroke, epilepsy, and traumatic brain injury [85].

Astrocytes express a variety of purinergic receptors, including P2X and P2Y receptors, which ATP and other purines activate. Purinergic signaling plays a role in regulating astrocyte function, neuron-glia communication, and neuronal survival. However, dysregulation of purinergic signaling can contribute to neurotoxicity. The excessive release of ATP from damaged neurons or activated astrocytes can lead to the overactivation of purinergic receptors on neurons, resulting in

excitotoxicity and neuronal damage [86]. Additionally, impaired purinergic signaling can disrupt the homeostatic balance between neurons and astrocytes, thereby further exacerbating neuronal vulnerability [87].

4.5 Metabolic Reprogramming Activated Astrocytes and Polarization

In response to CNS injury or disease, astrocytes can undergo polarization, a process that results in the formation of two distinct phenotypes: A1 (neurotoxic) and A2 (neuroprotective). Recent studies have suggested that metabolic reprogramming, a hallmark of activated astrocytes, plays a significant role in astrocyte polarization [88]. For instance, glycolytic metabolism has been shown to promote the A1 phenotype, while oxidative metabolism supports the A2 phenotype [89].

In addition to metabolic reprogramming, emerging fields such as exosome-mediated astrocyte-neuron communication mechanisms have gained increasing attention. Exosomes are extracellular vesicles that mediate intercellular communication by transferring various cargos, including miRNAs, between cells. Accumulating evidence suggests that astrocyte-derived exosomes can deliver miRNAs to neurons, thereby modulating neuronal function and survival [90]. However, the specific mechanisms underlying exosome-mediated astrocyte-neuron communication in the context of CNS injury or disease remain to be elucidated.

5. Therapeutic Implications

1. **Inhibiting Excessive Astrocyte Activation:** After TBI, astrocytes undergo morphological and molecular changes, becoming enlarged and adopting a 'reactive' phenotype. This excessive astrocyte activation, known as reactive astrogliosis, can be detrimental to neurons. Overactive astrocytes release pro-inflammatory cytokines, chemokines, and reactive oxygen species (ROS), which can exacerbate neuronal damage and inhibit repair [91]. While these factors can help initiate an immune response and promote repair, they can also cause neuronal damage if not adequately regulated. Targeting pathways involved in astrocyte activation, such as the JAK/STAT and NF- κ B pathways, could suppress overactivation and reduce neuroinflammation [92]. Drugs that block the production or activity of inflammatory mediators, such as COX-2 inhibitors and cytokine antagonists, can reduce astrocyte activation and limit neuroinflammation [93]. Agents that scavenge ROS or inhibit their production can protect neurons from oxidative damage caused by reactive astrocytes [94]. Drugs that target astrocyte-specific signaling pathways, such as gap junctions and purinergic receptors, can modulate astrocyte activation and reduce neurotoxicity [95]. Stem cells have been shown to have neuroprotective effects after TBI, including the ability to inhibit astrocyte activation and promote neuronal survival [96].

Several clinical trials are currently underway to evaluate the efficacy and safety of drugs inhibiting excessive astrocyte activation for the treatment of TBI. While results from these trials are still pending, early findings suggest potential therapeutic benefits. In summary of the above, the pharmacological approaches have been explored to inhibit excessive astrocyte activation after TBI. These include:

Minocycline: A tetracycline antibiotic, selective serotonin reuptake inhibitor (SSRI) with anti-inflammatory and neuroprotective properties. It has been shown to reduce astrocyte activation and improve functional outcomes in animal models of TBI [97].

Fluoxetine: A selective serotonin reuptake inhibitor (SSRI) antidepressant. It exerts anti-inflammatory effects in the brain, including inhibition of astrocyte activation [98].

Celecoxib: A nonsteroidal anti-inflammatory drug (NSAID) that inhibits cyclooxygenase-2 (COX-2), an enzyme involved in prostaglandin synthesis. COX-2 inhibition has been shown to reduce astrocyte activation and improve neurological function after TBI [99].

Pentoxifylline: A methylxanthine derivative that inhibits the production of inflammatory cytokines. It has been found to reduce astrocyte activation and improve blood flow in the injured brain [100].

Furthermore, Preclinical studies have demonstrated promising results for drugs inhibiting excessive astrocyte activation in preventing brain injury after TBI [101]. These drugs have been shown to reduce astrocyte activation and inflammation, protect neurons from damage, preserve cognitive function, improve motor and sensory function, and enhance neurogenesis and synaptogenesis. Estrogens, such as 17 β -estradiol (E2) and progesterone, play a neuroprotective role. These hormones are found in high concentrations in astrocytes, the star-shaped cells that support neurons [101]. Studies as reported by Michinaga et al. [102] in mice with traumatic brain injury (TBI) have shown that E2 therapy significantly reduces excessive astrocyte activation, leading to improvements in neurological function, decreased neuronal damage, and reduced brain swelling. Similarly, progesterone therapy in rats with TBI has been shown to reduce lesions, neuronal loss, and edema, while enhancing cognitive performance [103]. However, it's important to note that while estrogen treatment has shown promising results in these areas, it has not been found to improve TBI outcomes in all cases [102]. Further research is needed to understand the full potential and limitations of estrogen therapy for TBI. A promising therapeutic target for mitigating this glutamate surge is the peptide neurotransmitter N-acetylaspartylglutamate (NAAG), which suppresses glutamate transmission by activating presynaptic Group II metabotropic glutamate receptor subtype 3 (mGluR3). A study carried out by Zhong et al. [94] investigated the neuroprotective potential of a novel NAAG peptidase inhibitor, ZJ-43, in a rat model of moderate TBI and found that ZJ-43 significantly reduced neuronal degeneration and astrocyte loss in the hippocampus, a brain region highly vulnerable to TBI. This neuroprotection was observed at a dose of 50 mg/kg, where ZJ-43 was most effective. Notably, the protective effects of ZJ-43 were abolished entirely when co-administered with LY341495, a Group II mGluR antagonist, confirming that ZJ-43's neuroprotective effects are mediated through mGluR3 activation. Zhong et al. [104] suggest that ZJ-43, by inhibiting NAAG peptidase activity and prolonging the presence of synaptic NAAG, effectively reduces glutamate excitotoxicity and subsequent neuronal damage. The fact that ZJ-43 also reduced astrocyte loss (Table 1), which is essential for brain repair and support, further, highlights its potential therapeutic value.

2. **Promoting Beneficial Astrocyte Polarization:** Astrocytes can polarize into different phenotypes, each with distinct functional properties. A1 astrocytes are pro-inflammatory, while A2 astrocytes are anti-inflammatory and neuroprotective. Modulating polarization towards A2 astrocytes could promote neuroprotection. For example, activation of the Peroxisome proliferator-activated receptor gamma (PPAR γ) pathway has been shown to encourage polarization A2 and improve outcomes after brain injury [105, 106]. The peroxisome proliferator-activated receptor gamma (PPAR γ) pathway has emerged as a promising therapeutic target for TBI [106]. PPAR γ is a nuclear receptor that plays a crucial role in regulating inflammation, cell death, and neuroprotection [107]. Activation of PPAR γ has been

shown to have beneficial effects in various animal models of TBI, including reducing brain damage, improving cognitive function, and promoting neuronal survival [108, 109]. The neuroprotective effects of PPAR γ activation in TBI are mediated through multiple mechanisms, including Anti-Inflammatory effects, Anti-apoptotic effects, and Neurotrophic effects [110]. Synthetic PPAR γ agonists, such as rosiglitazone [106] and pioglitazone [109], have been shown to have neuroprotective effects in animal models of TBI. These agonists bind to PPAR γ and directly activate its transcriptional activity. Natural ligands, such as polyunsaturated fatty acids and endocannabinoids, can also activate PPAR γ . Supplementation with these ligands has been shown to improve cognitive function and reduce brain damage after TBI [111]. Gene therapy approaches, which involve delivering PPAR γ genes or small interfering RNAs (siRNAs) targeting PPAR γ inhibitors, have shown promise in preclinical studies. These approaches aim to modulate PPAR γ activity and enhance its neuroprotective effects [112].

3. **Enhancing Synaptic Function:** Astrocytes regulate synaptic activity through various mechanisms, including the release and reuptake of neurotransmitters. Hence, synaptic dysfunction is a central feature of TBI pathogenesis [113]. Synapses, the communication points between neurons, are highly vulnerable to mechanical and biochemical insults that occur during TBI [113]. Disruption of synaptic integrity and function leads to impaired neuronal communication and ultimately cognitive deficits [114]. In recent years, there has been growing interest in the development of therapeutic strategies that aim to enhance synaptic function after TBI. Preclinical studies have identified several potential targets for synaptic modulation, including Neurotrophic factors (BDNF and NGF), Synaptic adhesion molecules (N-cadherin), Ionotropic glutamate receptors (AMPA and NMDA receptors), and Synaptic scaffolding proteins [115]. Targeting astrocyte-specific molecules involved in synaptic plasticity, such as glutamate transporters and connexins, could restore normal synaptic function and improve cognitive outcomes [116].
4. **Augmenting Astrocyte Scavenging:** Astrocytes actively remove cellular debris and neurotoxic molecules from the CNS. Promoting astrocyte scavenging capacity could reduce the accumulation of harmful substances and protect neurons. Strategies to enhance astrocyte phagocytic activity include targeting scavenger receptors and lysosomal function [117].

Table 1 Therapeutic Implications of Targeting Astrocytes in TBI.

Therapeutic Target/Agent	Mechanism of Action	Observed Effects in Preclinical Studies	Reference
Minocycline	Inhibits inflammation, reduces astrocyte activation	Reduced astrocyte activation, improved functional outcomes	[97]
Fluoxetine	SSRI with anti-inflammatory effects inhibits astrocyte activation	Inhibition of astrocyte activation	[98]
Celecoxib	COX-2 inhibitor reduces prostaglandin synthesis	Reduced astrocyte activation, improved neurological function	[99]
Pentoxifylline	Inhibits inflammatory cytokine production	Reduced astrocyte activation, improved blood flow	[100]
Estrogen (E2)	Reduces astrocyte activation	Improved neurological function, decreased neuronal damage, and reduced brain swelling.	[102]
Progesterone	Unknown	Reduction in lesions, neuronal loss, and edema, while enhancing cognitive performance	[103]
ZJ-43 (NAAG peptidase inhibitor)	Inhibits NAAG peptidase, prolongs synaptic NAAG, and reduces glutamate excitotoxicity	Reduced neuronal degeneration and astrocyte loss in the hippocampus	[94, 104]
PPAR γ Agonists (Rosiglitazone, Pioglitazone)	Activates PPAR γ , reduces inflammation, and promotes neuroprotection	Reduced brain damage, improved cognitive function, and promoted neuronal survival	[106, 109]

Figure 2 demonstrates the efficacy of adenosine-conjugated lipid nanoparticles (Ad4 LNPs) for targeted delivery of siRNA against TLR4 to astrocytes following traumatic brain injury (TBI). Systemic administration of Ad4-siRNA LNPs resulted in the specific internalization of astrocytes, leading to a significant knockdown of TLR4 at both mRNA and protein levels in the brain (B). This TLR4 silencing modulated the inflammatory response, as evidenced by a decrease in pro-inflammatory cytokines and an increase in anti-inflammatory cytokines in serum (C). Furthermore, Ad4-LNP-mediated TLR4

knockdown attenuated TBI-induced blood-brain barrier (BBB) disruption, as shown by reduced dye leakage into the brain parenchyma (D). These findings suggest that Ad4 LNPs are a promising vehicle for astrocyte-specific delivery of nucleic acid therapeutics to mitigate neuroinflammation and secondary brain damage after TBI.

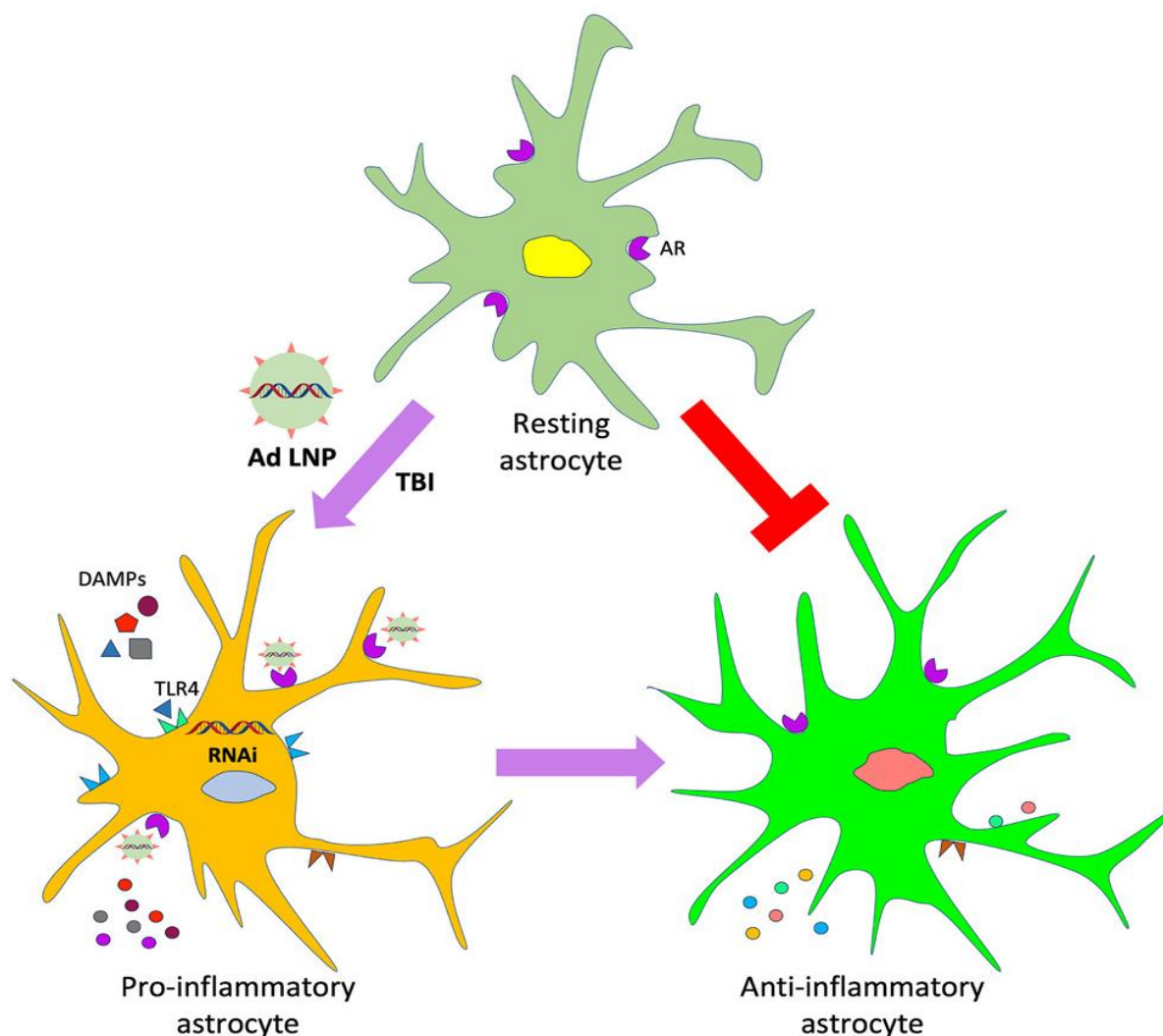


Figure 2 Adenosine-Conjugated Lipid Nanoparticles (Ad4 LNPs) for Targeted TLR4 Silencing in Astrocytes Attenuates TBI-Induced Inflammation and BBB Disruption.

6. Emerging Technologies Targeting Astrocytes

Beyond pharmacological and polarization strategies, emerging technologies hold considerable promise for TBI treatment by directly modulating astrocyte function. Gene editing techniques, most notably CRISPR-Cas9, hold promise for the precise manipulation of astrocyte gene expression. For example, studies have explored the use of CRISPR to downregulate GFAP (glial fibrillary acidic protein) expression in reactive astrocytes [118]. GFAP is a significant component of the astrocyte cytoskeleton, and its overexpression contributes to the formation of glial scars, which can inhibit axonal regeneration. Initial *in vitro* and *in vivo* studies have demonstrated the feasibility of using CRISPR-Cas9 to specifically target GFAP in astrocytes, leading to reduced GFAP expression and potentially mitigating glial scar formation after TBI [119]. Further research is needed to optimize

delivery methods and assess long-term effects, but this approach represents a significant step towards targeted astrocyte modulation.

Another promising avenue is the use of nanodelivery systems for targeted drug delivery to astrocytes. Conventional drug administration often results in off-target effects and limited drug penetration into the brain. Nanoparticles can be engineered to selectively target astrocytes by functionalizing their surface with ligands that bind to astrocyte-specific receptors or markers. For instance, nanoparticles coated with antibodies against the astrocyte-specific glutamate transporter GLT-1 have been shown to selectively deliver therapeutic payloads to astrocytes in *in vitro* and *in vivo* models of neurological disorders [120]. These payloads could include anti-inflammatory drugs, neurotrophic factors, or even gene-editing components. While the application of nanodelivery systems for astrocyte-targeted TBI treatment is still in its early stages, ongoing research is focused on developing biocompatible and biodegradable nanoparticles with enhanced targeting capabilities and controlled drug release profiles.

7. Conclusion

Astrocyte-neuron interactions play a critical role in the neuroinflammatory cascade of TBI. Reactive astrocytes release several pro-inflammatory mediators that can contribute to neuronal damage and exacerbate the neuroinflammatory cascade. Targeting astrocyte-neuron interactions is a promising therapeutic strategy for TBI. Several potential targets have been identified, including the inhibition of astrocyte activation, modulation of astrocyte-neuron signaling, and promotion of astrocyte-mediated neuroprotection. Further research is needed to validate these targets and to develop effective therapeutic interventions based on this approach.

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Author Contributions

Mega Obukohwo Oyovwi, Victor Oghenekparobo Emojevwe, Benneth BEN-AZU, Ejayeta E. Jeroh participated in sorting and conceptualizing the manuscript and wrote the manuscript. Mega Obukohwo Oyovwi, Victor Oghenekparobo Emojevwe, Benneth Ben-Azu, Ejayeta E. Jeroh organized the literature and presented ideas. Oyovwi Mega Obukohwo read and approved the submitted version. Mega Obukohwo Oyovwi, Victor Oghenekparobo Emojevwe, Benneth Ben-Azu, Ejayeta E. Jeroh is responsible for the contribution. The author contributed to the revision of the manuscript, read and approved the submitted version.

Competing Interests

The author declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AI-Assisted Technologies Statement

The author(s) used toolbaz for brainstorming and generating initial ideas related to the knowledge gap. The AI tool was used to explore different perspectives and potential research questions. The author(s) then refined and expanded upon these ideas using traditional research methods and critical analysis. The author(s) are fully responsible for the originality and accuracy of the final research presented and for any ethical implications.

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