Hypothesis

Neuroscience

Astrocytes
The Underlying Contributor to the Development of Autism

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Astrocytes, traditionally viewed as mere support cells in the central nervous system, have gained increasing recognition for their active roles in synaptic development, neurotransmission regulation, immune modulation, and neural circuitry refinement. Recent studies have implicated astrocyte dysfunction in a wide range of neurodevelopmental disorders, including autism spectrum disorder (ASD). This hypothesis article explores the proposition that astrocytes are not peripheral participants but central contributors to the pathophysiology of ASD. By examining the developmental roles of astrocytes, their interactions with neurons and microglia, and how their dysfunction might influence core features of autism such as impaired social communication, repetitive behaviors, and sensory sensitivities, this paper aims to reframe our understanding of autism's neurobiological roots. Incorporating evidence from animal models, human postmortem studies, genetic analyses, and neuroimaging, this article calls for a paradigm shift in autism research, highlighting astrocytes as potential diagnostic biomarkers and therapeutic targets.

Keywords: Astrocytes; Autism Spectrum Disorder; Neuronal Connections; Therapeutics; Neurobiology

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AUTISM spectrum disorder (ASD) encompasses a complex range of neurodevelopmental conditions characterized by persistent deficits in social interaction, communication, and restricted, repetitive patterns of behavior (Marinov et al., 2025). The prevalence of ASD has increased significantly over recent decades, partly due to improved diagnostics and awareness. Despite extensive research, the precise etiology of ASD remains elusive. Traditionally, autism has been considered a neuronal disorder, with a predominant focus on synaptic dysfunction, neural connectivity, and genetic mutations affecting neuronal pathways (Sauer et al., 2021). However, emerging evidence suggests that glial cells, particularly astrocytes, play a more dynamic and possibly primary role in the development and expression of ASD symptoms (Ilic & Sarajlija, 2025).

Astrocytes, the most abundant glial cell type in the human brain, were once thought to function solely in support of neurons by maintaining ion balance and nutrient supply (Xiong et al., 2023). Recent research has revealed that astrocytes are active participants in neurodevelopment, involved in synapse for-

mation and pruning, neurotransmitter uptake and release, modulation of the blood-brain barrier, and neuroimmune signaling (Liu et al., 2023). If astrocytes do not work properly in any of these roles during important stages of development, it can significantly impact how the brain grows and lead to signs of ASD (Gzieło & Nikiforuk, 2021).

The Developmental Role of Astrocytes in the CNS

Astrocytes appear during early brain development and influence neurogenesis, synaptogenesis, and gliogenesis. In fetal and early postnatal life, astrocytes secrete growth factors such as brain-derived neurotrophic factor (BDNF), transforming growth factor-beta (TGF-β), and thrombospondins, which are essential for the proliferation and differentiation of neurons (Kowiański et al., 2017). These factors also regulate the number and type of synapses that form, suggesting that astrocytes are gatekeepers of neural network architecture.

Astrocytes are also involved in synaptic pruning, a process vital for eliminating redundant or inappropriate synapses and refining neural circuits (Liu et al., 2021). This is particularly significant in ASD, where an overabundance of synapses has been observed in both human postmortem brains and animal models. Disrupted astrocytic pruning could underlie the hyperconnectivity and altered excitation-inhibition balance characteristic of autistic brains.

Astrocyte-Neuron Interactions in Synaptic Function

The concept of the "tripartite synapse" positions astrocytes as active components in synaptic transmission, along with presynaptic and postsynaptic neurons (Borroto‐Escuela et al., 2024). Astrocytes help control synaptic activity by taking in extra glutamate and GABA, keeping the right balance of ions outside the cells, and releasing substances like D-serine and ATP. In ASD, disruptions in glutamatergic and GABAergic signaling have been widely reported, with an imbalance favoring excitation over inhibition. Astrocytes not working properly might struggle to take in glutamate because they have fewer transporters like GLT-1 and GLAST, which can cause too much excitement in the brain and mess up how neural circuits work (Scimemi et al., 2013).

Moreover, astrocytes release extracellular vesicles containing proteins, lipids, and microRNAs that can influence neuronal gene expression and plasticity (Lawrence et al., 2023). Dysregulation in astrocyte-derived extracellular vesicles has been observed in individuals with ASD, further supporting their active role in neural communication and modulation.

Astrocytic Regulation of Neuroinflammation and Immune Responses

Neuroinflammation has been consistently associated with ASD, evident in elevated levels of proinflammatory cytokines such as IL-6, TNF-α, and IFN-γ in cerebrospinal fluid and brain tissue (Ramya et al., 2022). Astrocytes, in concert with microglia, mediate immune responses in the central nervous system. They can become reactive in response to environmental stimuli (e.g., infection, maternal immune activation) and release inflammatory mediators that affect neurodevelopment.

In mouse models of maternal immune activation, offspring show altered astrocytic morphology and gene expression patterns consistent with ASD phenotypes (Han et al., 2021). These reactive astrocytes secrete cytokines that disrupt the blood-brain barrier and neuronal development. Chronic astrocyte activation during development may contribute to the persistent neuroinflammatory state observed in autism.

Genetic Evidence Linking Astrocytes to Autism

Recent genome-wide association studies (GWAS) and transcriptomic analyses have identified several ASD-associated genes preferentially expressed in astrocytes (Matta et al., 2019). For example, mutations in MECP2, a gene implicated in Rett syndrome (an ASD-related disorder), lead to profound astrocytic dysfunction (Vakilzadeh et al., 2022). When MECP2 is specifically removed from astrocytes in mouse models, it causes important symptoms of the disorder, like problems with social interactions and unusual dendrite shapes (Ehinger et al., 2021).

Other genes such as FMR1 (fragile X mental retardation 1), SHANK3, and TSC1/2, although traditionally considered neuronal, also impact astrocyte function (Xia & Xu, 2022). These genes regulate pathways involved in mTOR signaling, protein synthesis, and synaptic plasticity, all of which are critical for astrocytic support of neural circuits.

Astrocytes and Sensory Processing in ASD

Sensory processing abnormalities are a core feature of ASD, often manifesting as hypersensitivity or hyposensitivity to tactile, auditory, or visual stimuli (Cresto et al., 2019). Astrocytes play a role in the modulation of sensory input through regulation of neurotransmission in thalamocortical and corticospinal pathways. In studies with rodents that have ASD, changes in how astrocytes handle calcium signals have been seen in areas of the brain that process sensory information (Wood et al., 2021), which relates to unusual sensory behaviors (Rabindran et al., 2020).

Astrocytes also influence the maturation of sensory maps during critical periods of development. Dysregulated astrocytic signaling may result in improperly tuned sensory circuits, contributing to the atypical perceptual experiences seen in autism.

Neuroimaging and Postmortem Evidence of Astrocyte Involvement in ASD

Magnetic resonance spectroscopy (MRS) studies have reported altered levels of glial markers such as myo-inositol in the brains of individuals with ASD, suggesting astrocyte involvement (Vakilzadeh et al., 2022). Positron emission tomography (PET) imaging using ligands for glial fibrillary acidic protein (GFAP) has also demonstrated increased astrocytic activation in key brain regions (Pereira et al., 2024).

Postmortem examinations of autistic brains reveal increased astrocyte density and altered expression of astrocyte-specific genes (Matta et al., 2019). In particular, increased GFAP expression and morphological changes indicative of reactive gliosis have been consistently reported, supporting the idea of chronic astrocyte activation in ASD.

Therapeutic Implications and Future Directions

If astrocytes are indeed central to ASD pathogenesis, they present novel therapeutic targets (Matta et al., 2019). Modulating astrocyte function could restore synaptic balance, reduce neuroinflammation, and normalize sensory processing. Compounds that enhance astrocytic glutamate uptake or modulate calcium signaling are currently under investigation in preclinical models.

Stem cell-derived astrocytes from individuals with ASD offer a promising platform for drug screening and personalized medicine (Allen et al., 2022). Moreover, gene therapy approaches targeting astrocyte-specific pathways may provide more precise interventions than traditional neuron-centric strategies.

Conclusion

This hypothesis proposes that astrocytes are not passive bystanders but active participants in the neurodevelopmental processes that give rise to autism. Through their roles in synapse formation, neurotransmission, immune regulation, and sensory integration, astrocytes influence nearly every aspect of brain development implicated in ASD. Understanding astrocyte dysfunction could unlock new diagnostic and therapeutic possibilities and fundamentally shift the way we conceptualize and treat autism spectrum disorders.■

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