Advances in the Study of Astrocyte Extracellular Vesicles in Post-Stroke Cognitive Impairment: Postprint

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Abstract

Post-stroke cognitive impairment (PSCI) represents a common complication in stroke patients, characterized by cognitive dysfunction that directly impacts quality of life. Previous studies have identified astrocytes as playing a crucial role in PSCI pathogenesis. Additionally, extracellular vesicles (EVs) have been established as important mediators of intercellular communication, participating in various pathophysiological processes through the carriage and transport of diverse cargo. Astrocyte-derived extracellular vesicles (ADEVs) may communicate with other brain cells and ameliorate PSCI via processes including enhanced synaptic plasticity, regulation of neuroinflammation, and modulation of angiogenesis and autophagy. This review elucidates the multifaceted effects of ADEVs on PSCI development, provides novel strategies for investigating the underlying mechanisms of PSCI, and further explores the potential utility of ADEVs as innovative therapeutics and biomarkers for the diagnosis and treatment of PSCI.

Full Text

Preamble

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Research Progress of Astrocyte-Derived Extracellular Vesicles in Post-Stroke Cognitive Impairment

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Abstract

Post-stroke cognitive impairment (PSCI), characterized by cognitive dysfunction, is a common complication of stroke that directly impacts patients' quality of life. Previous studies have demonstrated that astrocytes play a crucial role in the pathogenesis of PSCI. Additionally, extracellular vesicles (EVs) have been recognized as important mediators of intercellular communication, participating in various pathophysiological processes by carrying and transporting diverse cargo. Astrocyte-derived extracellular vesicles (ADEVs) may communicate with other brain cells to ameliorate PSCI by enhancing synaptic plasticity, modulating neuroinflammation, regulating angiogenesis, and controlling autophagy. This review elucidates the multifaceted effects of ADEVs on PSCI development, offers novel strategies for investigating the underlying mechanisms of PSCI, and explores the potential of ADEVs as innovative therapeutic agents and biomarkers for the diagnosis and treatment of PSCI.

Keywords: Stroke; Cognitive Disorders; Astrocyte-Derived Extracellular Vesicles; Synaptic Plasticity; Neuroinflammation

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Main Text

Post-stroke cognitive impairment (PSCI) represents a major sequela of cerebral stroke, involving multiple cognitive domains but primarily characterized by pronounced deficits in executive function, processing speed, and attention. The pathological damage in PSCI, including apoptosis, oxidative stress, inflammatory responses, alterations in neurotrophic factor levels, and changes in gene expression, further impacts synaptic plasticity. Recent studies indicate that extracellular vesicles (EVs) may play a potential role in these pathogenic processes. Astrocytes, well-known for their central role in the central nervous system, are primarily responsible for maintaining brain homeostasis and influencing the function of various CNS cells by releasing diverse mediators such as enzymes, cytokines, and neurotrophic factors [1]. Astrocyte-derived extracellular vesicles (ADEVs) constitute one of the important pathways through which astrocytes accomplish these tasks. This review will clarify the connection between ADEVs and PSCI and discuss the therapeutic potential of ADEVs in PSCI.

Literature Search Strategy: We conducted a computerized search of PubMed, Web of Science, CNKI, and Wanfang Data Knowledge Service Platform from inception to May 2023. Chinese search terms included "stroke," "cognitive impairment," "astrocyte-derived extracellular vesicles," "synaptic plasticity," and "neuroinflammation." English search terms included "stroke," "cognitive impairment," "astrocyte-derived extracellular vesicles," "synaptic plasticity," and "neuroinflammation." Inclusion criteria comprised literature addressing the effects of ADEVs on PSCI and their therapeutic potential. Exclusion criteria included irrelevant literature, low-quality studies, and articles without full-text availability. A total of 48 articles were ultimately included.

1.1 Synthesis of EVs

EVs are double-membrane-enclosed nanoscale vesicles that deliver various active molecules—including proteins, lipids, and nucleic acids—from donor cells to specific target cells. Secreted by multiple cell types including astrocytes into the extracellular space, EVs participate in intercellular communication. Based on their size and origin, EVs are classified into three categories: exosomes (30–150 nm in diameter), microvesicles (100–1,000 nm), and apoptotic bodies (1,000–5,000 nm) [2]. Exosomes originate as intraluminal vesicles within multivesicular bodies (MVBs) generated by the endosomal sorting complex required for transport (ESCRT). Microvesicles arise from plasma membrane budding, while apoptotic bodies are fragments produced during cell disintegration. All three types are collectively referred to as EVs in this review. EV biogenesis occurs through

two major pathways: ESCRT-dependent and ESCRT-independent mechanisms. The ESCRT machinery, composed of 21 complexes, drives inward budding of endosomal membranes for cargo segregation and sorting. ESCRT-independent pathways for EV biogenesis are numerous but less well-characterized. One ESCRT-independent mechanism involves cluster of differentiation 63 (CD63), a tetraspanin protein highly expressed on EV surfaces [3].

1.2 Cargo of ADEVs

EVs were once considered cellular waste products, but are now known to participate in intercellular communication under both physiological and pathological conditions, regulating homeostatic signaling or triggering cytotoxic responses in target cells [4]. Astrocytes can be activated and differentiate into distinct subtypes under various conditions, including neurotoxic/pro-inflammatory phenotypes and neuroprotective/anti-inflammatory phenotypes that exert opposing effects on disease progression [5]. ADEVs exhibit similar plasticity, with their cargo varying according to environmental conditions but typically comprising proteins, lipids, and nucleic acids.

On one hand, EVs released by astrocytes support and protect neurons and synapses, playing important roles in preventing conditions such as Alzheimer's disease (AD) and CNS injury [6]. Astrocytes cultured under normal conditions secrete EVs containing neuroprotective molecules such as heat shock proteins (HSPs), α-synuclein (α-Syn), low-density lipoprotein receptor-related protein-1 (LRP-1), and apolipoprotein E (ApoE), as well as proteins that positively regulate neuronal excitability and synaptic development—including potassium channel tetramerization domain-containing 12 (KCTD-12), glucose-6-phosphate dehydrogenase (G6PD), and kinesin family member 5B (KIF5B)—which can inhibit stress-induced neuronal apoptosis and senescence [7]. Recent studies have identified microRNAs (miRNAs) secreted via ADEVs, such as miR-124, miR-9, miR-128, and miR-137, that regulate different stages of adult neurogenesis. As the most abundant miRNA in the brain, miR-124 ectopic expression significantly reduces neuronal death and infarct volume in middle cerebral artery occlusion (MCAO) rats, improving both motor and cognitive function [8].

On the other hand, ADEVs released under certain pathological conditions have been implicated in propagating pathological proteins and promoting disease progression. The causal relationship between cerebral amyloid-β (Aβ) deposition and PSCI after stroke remains uncertain and controversial, but chronic inflammation may indirectly promote Aβ production in neurons by enhancing the release of casein kinase 1 (CK1)-enriched ADEVs [9].

2 Connection Between ADEVs and PSCI

2.1 ADEVs and Synaptic Plasticity

Synaptic plasticity refers to activity-dependent changes in synaptic connection strength and transmission efficiency within pre-existing synapses, which can be

structural or functional. Alterations in synaptic plasticity have been shown to play a critical role in both the development and treatment of PSCI. Increased synaptic connection strength and enhanced transmission efficiency directly up-regulate information processing and storage capacity within the CNS, thereby improving cognitive function [10].

Neurons undergo profound transcriptomic changes during the subacute phase after stroke, enabling plasticity modifications. ADEV-mediated intercellular signaling transmits signals to neurons to activate regenerative mechanisms and exert protective effects on synaptic plasticity. Transforming growth factor-β (TGF-β), a synaptogenic factor secreted by astrocytes, increases excitatory synapse formation. ADEVs carrying fibrillin-2 (FBN2) on their surface activate TGF-β signaling in neurons, promoting dendritic spine and synapse formation [6]. PROIA et al. [11] demonstrated that primary rat ADEVs carry fibroblast growth factor 2 (FGF-2) and vascular endothelial growth factor (VEGF). FGF-2, a single-chain polypeptide containing 146 amino acids, enhances synaptic plasticity after cerebral ischemia/reperfusion injury through the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA)/cAMP response element-binding protein (CREB) pathway mediated by salidroside [12]. During chronic cerebral hypoperfusion (CCH), VEGF enhances presynaptic function by increasing neurite outgrowth, promoting neurite extension, and elevating expression of growth-associated protein-43 (GAP-43) and synaptophysin (SYN), thereby improving impaired hippocampal synaptic plasticity and alleviating cognitive dysfunction [13].

Excessive reactive oxygen species (ROS) generated after stroke can impair synaptic plasticity through various mechanisms, including damage to dendritic spines, neurons, or brain repair mechanisms, leading to loss of synaptic connectivity and information processing capacity and contributing to PSCI pathogenesis [14]. G6PD carried by ADEVs is essential for nicotinamide adenine dinucleotide phosphate (NADPH) regeneration and plays a central role in protecting against ROS-induced cellular oxidative stress, suggesting that ADEVs may prevent ROS-mediated pathological changes [15]. Additionally, under oxidative stress conditions, SYN is released by astrocytes via EVs to promote neurite growth, neuronal survival, and improved synaptic plasticity [16]. However, some studies have shown beneficial effects from ADEV inhibition. HIRA et al. [17] demonstrated that inhibiting semaphorin 3A (Sema3A) during the subacute phase of stroke impedes astrocyte activation and promotes axonal growth and functional recovery in stroke rats through negative regulation of miR-30c-2-3p and miR-326-5p in ADEVs via prostaglandin D synthase (PGDS).

Meta-analyses of the ADEV proteome have identified additional proteins that regulate axonal growth and guidance, including β-tubulin (TUBB), actin gamma 1 (ACTG1), Ras homolog gene family member A (RhoA), and reticulon protein 4 (RTN4) [18]. In summary, ADEVs play a crucial role in maintaining synaptic plasticity, and appropriate modulation of ADEVs may represent a novel target for improving PSCI.

2.2 ADEVs and Neuroinflammation

Activation of neuroinflammation in the hippocampus is critical for PSCI development. Neuroinflammation preferentially impairs higher-order cognitive and executive functions in the prefrontal cortex, promotes neuronal death, and exacerbates functional deficits, closely correlating with PSCI pathophysiology. Astrocytes become activated within hours after cerebral ischemia and serve as key regulators of the inflammatory response [19].

Recent years have witnessed growing interest in the effects of ADEVs on adult neurogenesis. On one hand, ADEVs can promote CNS disease by inducing neuroinflammation and neurotoxicity. IBÁÑEZ et al. [20] reported that Toll-like receptor 4 (TLR4)-mediated ADEVs are released as part of the neuroinflammatory process, and TLR4 knockout reduces the accumulation of pro-inflammatory proteins and miRNAs in mouse ADEVs. Under lipopolysaccharide (LPS)-induced stress conditions, rat astrocytes shed EVs containing miR-34a, which targets and reduces translation of the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2), thereby sensitizing neurons to toxic injury [21]. Bioinformatic analysis revealed that under tumor necrosis factor-α (TNF-α) and interleukin (IL)-1β stimulation, ADEVs carry miR-125a-5p and miR-16-5p that target neurotrophin receptor kinase 3 (NTRK3) and its downstream effector Bcl-2, inhibiting neurotrophic signaling in neurons—potentially representing a protective response against brain inflammation [22].

On the other hand, ADEVs can alleviate inflammation/apoptosis and improve neuroplasticity. Apolipoprotein D (ApoD), primarily expressed in the nervous system in response to oxidative stress, is secreted via EVs from human astrocyte cell line 1321N1 and mouse primary astrocytes. These ApoD-containing EVs maintain cell survival by controlling ROS accumulation and levels of lipid peroxides generated during aging or pathological conditions [23]. Further research indicates that controlling ROS and lipid peroxide accumulation can mitigate ferroptosis, alleviate stroke-induced damage, and improve cognitive impairment [24]. GUITART et al. [25] found that mouse primary astrocytes exposed to ischemic and oxidative stress conditions release EVs containing elevated levels of prion protein (PrP)—a cell surface glycoprotein that mediates neuroprotection under oxidative stress—which in turn prevents neuronal death under hypoxic and ischemic conditions. Moreover, berberine can alleviate neuroinflammation by increasing miR-182-5p levels in ADEVs secreted after stroke, acting on Ras-related C3 botulinum toxin substrate 1 (Rac1) in damaged neurons [26].

Collectively, these findings demonstrate that inflammatory responses regulate adult neurogenesis and may exert dual roles depending on context. Therefore, targeting ADEVs to suppress neuroinflammation after ischemic stroke represents a potentially effective strategy for improving PSCI.

2.3 ADEVs and Other Pathogenic Mechanisms

The pathogenesis of PSCI is highly complex. Beyond the aforementioned roles, ADEVs may also participate in regulating pathophysiological processes such as autophagy and angiogenesis during PSCI development.

Autophagy is a highly conserved catabolic pathway in cells that degrades harmful proteins and damaged organelles through lysosomal digestion. Importantly, autophagy plays a significant role in neuronal injury and cognitive decline [27]. ADEVs preconditioned with oxygen-glucose deprivation (OGD) transfer circular RNA SHOC2 (circSHOC2) to neurons, acting on the miR-7670-3p/Sirtuin 1 (SIRT1) axis to inhibit neuronal apoptosis and improve neuronal injury by enhancing autophagy [28]. Furthermore, ADEVs can suppress autophagy, alleviate OGD-induced mouse neuronal apoptosis, and downregulate expression of TNF-α, IL-6, and IL-1β, thereby enhancing neuronal defense against ischemic stroke and reducing cerebral infarct volume [29].

Angiogenesis, the process of new microvessel branching from pre-existing vessels, plays a crucial role in stroke recovery by delivering blood flow and metabolic nutrients to injured regions, promoting neural tissue repair through enhanced neurogenesis and synaptic connectivity, thereby influencing PSCI [30]. FGF-2 and VEGF secreted by ADEVs are not only involved in synaptic plasticity but also promote angiogenesis in the cerebral cortex, protecting neuronal structure and function and significantly improving spatial learning and memory in rats [31].

Mitochondria are highly dynamic organelles that regulate metabolism, cell death, and energy production. Maintaining mitochondrial function is essential for improving PSCI [32]. The balance of mitochondrial fusion, fission, and mitophagy characterizes mitochondrial quality control. Recently, mitochondria-derived vesicles (MDVs) have been identified as a novel mechanism for mitochondrial quality control, mediating cargo transport between mitochondria and other organelles.

The aforementioned studies collectively demonstrate that ADEVs exert neuroprotective effects through multiple pathways, positioning them as potential therapeutic targets for PSCI. The potential roles of ADEVs in PSCI treatment are illustrated in Figure 1 [Figure 1: see original paper] and Table 1 .

3.1 ADEVs and MDVs

The release of damaged mitochondria, mitochondrial N-formyl peptides (NFPs), and mitochondrial DNA (mtDNA) can serve as damage-associated molecular patterns (DAMPs) that activate the innate immune system and exacerbate neuroinflammation [33]. Cells selectively target DAMPs for lysosomal degradation to prevent release of these pro-inflammatory substances into EVs, a process dependent on MDVs. Whether mitochondrial components are directed to lysosomes or EVs depends on two distinct MDV pathways: sorting nexin 9 (SNX9)

and optic atrophy protein 1 (OPA1) participate in loading mitochondrial cargo into EVs [34], whereas MDVs dependent on the PTEN-induced putative kinase 1 (PINK1)/Parkin pathway are degraded by lysosomes [35]. Studies have confirmed that ADEVs are indeed associated with MDVs. For example, mitochondrial dysfunction in mice can be monitored by measuring the depletion of mitochondrial components in ADEVs [36]. Interestingly, pathological conditions in the lungs can also affect the brain via ADEVs. PELUSO et al. [37] demonstrated highly abnormal expression of mitochondrial proteins in neuron-derived EVs and ADEVs from COVID-19 patients with neurological manifestations, with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) inducing neuropsychiatric alterations through this mechanism.

Recent studies have revealed that mitochondrial DAMPs are highly enriched within EVs, propagating neuroinflammation and contributing to neurodegenerative diseases [38]. EVs isolated from astrocytes exposed to Aβ and oxidative stress show the presence of mitochondrial proteins and mtRNA, suggesting that ADEVs export harmful mitochondrial components, leading to cellular pathology and AD [39]. Encapsulating mitochondrial DAMPs within EVs has been reported as a coping mechanism to prevent release of free mitochondrial DAMPs that would otherwise participate in inflammatory responses [34]. In summary, selective packaging of mitochondrial DAMPs into ADEVs may reduce neuroinflammation and represent a potential target for improving PSCI. Beyond secreting mitochondrial DAMPs, astrocytes can also shed EVs containing functional mitochondria that promote neuronal survival and enhance neuroplasticity in the mouse hippocampus, contributing to cognitive improvement [40-41].

Although accumulating evidence indicates that MDVs are secreted as a subset of EVs, the underlying mechanisms remain unknown. Further research on the connection between MDVs and EVs is needed to fully harness the therapeutic potential of EVs. In conclusion, MDVs, as a newly identified mitochondrial quality control mechanism, may serve a dual role in preventing inflammation and ensuring that astrocytes transfer only functional mitochondria by selectively regulating the packaging of mitochondrial DAMPs into ADEVs, offering a novel target for PSCI mitigation.

3.2 ADEVs as Novel Therapeutics and Biomarkers

The primary clinical treatment for ischemic stroke currently involves pharmacological agents such as tissue plasminogen activator, edaravone, and aspirin. However, most small-molecule drugs and nearly all macromolecular drugs cannot cross the blood-brain barrier (BBB) due to its low permeability, hindering therapeutic progress for ischemic stroke.

Recently, biomimetic drug delivery systems (BDDS) developed by directly utilizing or mimicking biological structures have provided promising approaches to overcome drug delivery obstacles in the brain [42]. Transmission electron microscopy has demonstrated EV release from astrocytic end-feet, with these

vesicles subsequently crossing endothelial cells via transcytosis and being released into small vessels in both in vitro models and mouse models of focal brain injury [43]. Therefore, ADEVs capable of crossing the BBB are considered excellent candidates for developing peripheral non-invasive drug carriers. miR-92b-3p, an oncomiR, has been shown to significantly reduce phosphatase and tensin homolog (PTEN) levels and activate the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT) signaling pathway—one of the most important pathways regulating cell survival and proliferation. EVs released from OGD-preconditioned astrocytes shuttle miR-92b-3p to neurons, improving cell death and apoptosis and facilitating axonal growth [44]. Moreover, in vivo studies have found that rats with brain injury treated with ADEVs exhibit better motor coordination in rotarod tests and improved cognitive function in water maze tests [45]. Thus, ADEV-mediated delivery of nucleic acid cargo may ameliorate PSCI.

The BBB-penetrating capability of ADEVs also positions them as potential biomarkers for PSCI. Despite continuous development of new diagnostic and prognostic methods for PSCI, early detection and outcome prediction remain challenging. Biomarkers can facilitate PSCI diagnosis; one analysis of 13 stroke studies examining 15 circulating biomarkers identified five miRNAs (miR-132, let-7i, miR-140-5p, miR-22, and miR-221-3p) that were upregulated in PSCI patients [46]. To date, various disease-associated molecules have been identified in ADEVs, including β-site amyloid precursor protein cleaving enzyme 1 (BACE-1), γ-secretase, soluble A$ $42, soluble amyloid precursor protein (APP) β, and complement proteins, which may serve as potential markers of cognitive impairment [47]. Furthermore, after diffusing across the BBB to the periphery, ADEVs can be selectively captured using antibodies targeting glutamate-aspartate transporter (GLAST), a membrane protein specifically present on astrocytes and ADEVs [48]. This approach substantially simplifies the isolation of ADEVs from patient serum/plasma and screening for potential biomarkers within ADEVs.

As described above, ADEVs improve synaptic plasticity through intercellular signaling, mediate neuroinflammation by secreting inflammatory mediators, and participate in pathophysiological processes such as autophagy and angiogenesis, making them potential therapeutic targets for PSCI. Additionally, the intricate connection between ADEVs and MDVs represents a potential area for mitochondrial quality control. On the other hand, given their advantages of stability in blood, BBB penetrability, and targeting of specific brain cells, ADEVs can be harnessed to deliver therapeutic cargo to the CNS. Designing and engineering ADEVs with beneficial effects represents a promising strategy, and screening ADEV cargo for biomarkers to diagnose PSCI will benefit patient rehabilitation and prognosis.

The role of ADEVs in neurodegenerative diseases is increasingly recognized, and modulating the communication between ADEVs and neurons and other cells may influence PSCI pathophysiology. However, due to the diversity of ADEVs

and the complexity of PSCI pathogenesis, further investigation is needed to elucidate the detailed mechanisms of ADEV action in PSCI. To provide safer, more specific, and more potent therapeutic options, future research directions may involve improving EV engineering technology to modulate ADEV cargo for carrying desired biomolecules, or even developing advanced technologies to artificially synthesize ADEVs with therapeutic cargo based on comprehensive understanding of ADEV composition and function, opening a new frontier for next-generation PSCI therapeutics.

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