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REVIEW

Revisiting Vesicle Trafficking in Astrocytes

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ABSTRACT: Astrocytes contribute to central nervous system (CNS) homeostasis by taking up and releasing various transmitters, ions, water, and energy molecules, thereby modulating neuronal function and maintaining the blood-brain barrier. The dynamic delivery, retrieval, and recycling of transporters, channels, receptors, and vesicular cargo at the astrocyte plasma membrane are regulated by the cytoskeleton networks composed of microtubules, actin filaments, and intermediate filaments. Increasing evidence indicates that changes in vesicle trafficking disrupt astrocyte–neuron communication and contribute to CNS dysfunction in pathological conditions. This review presents recent findings on vesicle trafficking in astrocytes with emphasis on the cytoskeletal mechanisms that govern vesicle mobility and membrane availability of key transporters, channels, and receptors. We also discuss the trafficking of neuroactive peptides, gliotransmitters, and neurotropic pathogens within astrocytes. This review highlights vesicle trafficking as a central regulator of astrocyte function and CNS homeostasis and identifies critical gaps that remain to be addressed.

KEYWORDS: Glia; astrocyte; vesicle trafficking; cytoskeleton; cytolinker; transporter; channel; receptor

1 Introduction

Astrocytes are glial cells that play a crucial role in the functioning of the central nervous system (CNS) in healthy and pathological conditions. The uptake and release of various molecules and ions through transporters and channels in their plasma membrane, as well as the trafficking of different endogenous and exogenous molecules and the detection of pathogens by receptors, contribute to maintaining the functions of neighboring neurons and other glial cells, as well as to sensing neurotropic infections [1,2].

In eukaryotic cells, protein synthesis in the endoplasmic reticulum is followed by trafficking of intracellular vesicles via the Golgi apparatus and sorting to different cellular destinations, including the endo-lysosomal system and the plasma membrane [3]. To fulfil their role at the plasma membrane, transporters and receptors must be delivered to the cell periphery after translation. This is achieved by their incorporation into membrane-bound intracellular secretory vesicles, which then undergo fusion with the plasma membrane. To maintain a balanced number of transporters and receptors and preserve normal astrocyte and CNS function, astrocytes rely on several coordinated processes, including transcription, translation, vesicle packaging, transport along the cytoskeleton, and exocytotic fusion with the plasma membrane. The turnover of plasma membrane transporters and receptors is also regulated by endocytosis, which removes them from the plasma membrane. In some cases, transporters and receptors are recycled to the plasma membrane, while others are targeted for degradation. The translocation of intracellular

vesicles between the cytosol and cell membranes is regulated by various proteins, such as RAB GTPases (RABs) and GDP dissociation inhibitors (GDIs), which mediate GDP/GTP exchange and thus regulate the functional status of RABs. RABs and GDIs together coordinate intracellular membrane trafficking, including endocytosis, the process by which cells internalize extracellular material, ligands, and plasma membrane proteins and lipids [4]. In astrocytes, changes in the function of these regulatory proteins affect vesicle recycling, as well as the molecular interactions that determine directional vesicle mobility, involving motor proteins and the cytoskeleton. Given the multiple roles of astrocytes in the homeostatic support of neurons, alterations in intracellular vesicle trafficking in astrocytes may contribute to CNS malfunction [2].

Besides intracellular vesicles, the functions of astrocytes and neighboring cells are also affected by molecules that are transported within extracellular vesicles (EVs), yet this topic is far less understood. EVs are a heterogeneous group of membrane-bound vesicles; their cargo is often very diverse and it includes nucleic acids, lipids, and proteins [5]. An increasing number of studies indicate that EVs can modulate various diseases, including neurological disorders. Similar to the transport of intracellular vesicles, transport, docking, and fusion of EVs with the plasmalemma is mediated by the cytoskeleton along with their molecular motors and regulatory proteins [6].

Mobility of vesicles within astrocytes critically depends on all three types of the cytoskeleton [7]. In addition to microtubules and actin filaments, along which molecular motors drive vesicle movements, intermediate filaments (IFs) in neuronal cells have also been shown to influence the directionality and speed of vesicle dynamics [7]. Different types of IFs preferentially interact with either microtubules or actin filaments, primarily through molecular motors and multidomain IF-associated proteins such as cytolinker plectin [8]. In astrocytes, detailed investigation of vesicle dynamics along the cytoskeleton began roughly twenty years ago. It is now widely accepted that vesicle trafficking is essential for astrocyte-to-neuron communication [7], yet this field continues to evolve as remaining gaps in knowledge are addressed. Most of our knowledge on vesicle trafficking comes from studies in primary murine astrocytes, with comparatively less known about human astrocytes. The aim of this review is to summarize recent findings predominantly on intracellular vesicle trafficking in astrocytes, covering the most studied plasma membrane and vesicular transporters, channels, receptors, and specific vesicle cargo.

2 Distribution of Transporters and Receptors in Astrocytes Is Affected by Vesicle Trafficking

2.1 Glutamate Transporters in the Plasma Membrane of Astrocytes

Every plasma membrane transporter is, at certain stages of its life cycle, transported by membrane-bound vesicles in the cytoplasm (Fig. 1). Among the best-studied plasma membrane transporters in astrocytes that are trafficked in vesicles are glutamate transporters from the solute carrier 1 (SLC1) family of transmembrane proteins, which regulate synaptic clearance of the excitatory neurotransmitter glutamate (Table 1). Glutamate is the main excitatory neurotransmitter and regulates cognition, mood, and synaptic activity in key brain regions such as the hippocampus, prefrontal cortex, and amygdala [9]. Uptake of glutamate from the synaptic cleft into neurons and astrocytes occurs through excitatory amino acid transporter 1 (EAAT1; the human homologue of GLAST1), which is highly expressed in astrocytes, and through EAAT2 (the human homologue of GLT1), which is the most abundant glutamate transporter in the brain [10]. After synthesis within the endoplasmic reticulum in both neurons and astrocytes, these transporters are trafficked to the plasma membrane. In astrocytes, it has been shown that upon reaching the plasma membrane, EAAT1 undergoes surface diffusion, which is sensitive to neuronal and glial activities [11]. A sufficient number of EAAT1 transporters in the plasma membrane of astrocytes contributes to glutamate transmission at synapses by limiting its diffusion [11]. In astrocytes, EAAT1 is constitutively trafficked

between the plasma membrane and endosomes via an endocytosis/recycling pathway, congregating in clusters within early and recycling endosomes and partly in lysosomes [10]. Studies in cultured astrocytes show that secretory vesicles containing recombinant fluorescently tagged EAAT2 display mobility patterns similar to other secretory vesicles, suggesting they use similar microtubule-based transport machinery [7,12]. After reaching the cell periphery, vesicles carrying EAAT fuse with the plasma membrane via calcium-dependent exocytosis and acquire an uneven distribution within the plasma membrane, as reported for EAAT2 in primary rat astrocytes [7]. The density of transporters in the plasma membrane affects glutamate uptake, as reported in rat and mouse astrocytes. Similar to EAAT1, it has also been demonstrated for EAAT2 that this is significantly affected by endocytosis [7]. The uptake of glutamate prevents excitotoxicity by maintaining extracellular glutamate concentration at low nanomolar levels and by restricting glutamate diffusion away from the synaptic cleft [11].

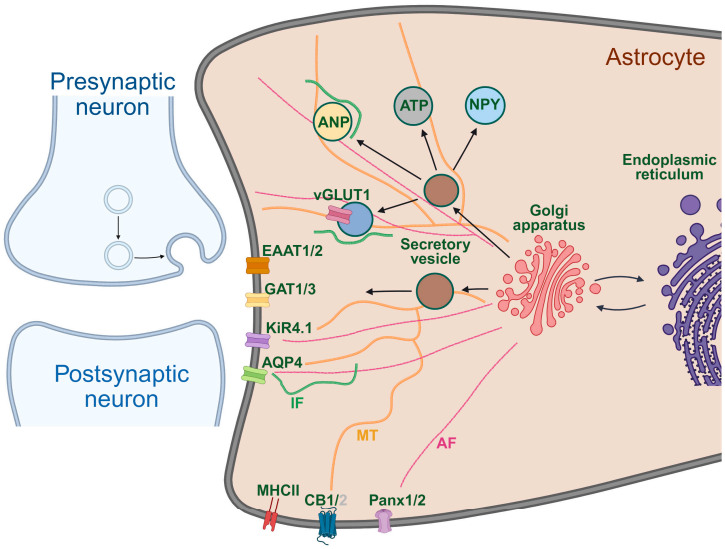

Figure 1: Schematic of vesicle trafficking in astrocytes, showing secretory pathways for plasma membrane proteins (transporters, channels, receptors) and vesicle cargo (peptides, ATP). Trafficking of exocytotic vesicles in astrocytes has been studied for: AQP4, aquaporin 4 water channel (transport of water); EAAT1/2, excitatory amino acid transporter type 1 and 2 (glutamate (glu) uptake); GAT1/3, GABA transporter type 1 and 3 (uptake of GABA); Kir4.1, inwardly rectifying potassium channel Kir4.1 (uptake of K^+); Panx1, pannexin 1 (ATP release); Panx2, pannexin 2 (unclear role in astrocytes); vGLUT1, vesicular glutamate transporter 1 (uptake of glutamate into vesicles); CB1 receptor, cannabinoid receptor type 1 (detection of endogenous and exogenous cannabinoids); and MHCII, major histocompatibility complex class II (presents processed antigens). In addition, trafficking of the following signaling molecules has been studied in astrocytes: ANP, atrial natriuretic peptide; NPY, neuropeptide Y; ATP, adenosine triphosphate. These processes critically depend on vesicle traffic along microtubules (MT) and actin filaments (AF), while intermediate filaments (IF) have also been shown to influence them. Note that the CB2 receptor (in grey) has only been detected in astrocytoma, and it remains unclear if its expression is not restricted to infiltrating microglia or macrophages. Created in BioRender (https://BioRender.com/te8mf3e).

Excessive delivery of EAAT transporters to the plasma membrane, together with deregulation of endocytosis and recycling of EAATs from the plasma membrane, results in excessive concentrations of glutamate in the synaptic cleft [13]. Disruption of glutamate uptake causes excitotoxicity and leads to neuronal damage, which is recognized in several neurodevelopmental, psychiatric, and substance-use disorders (recently reviewed in [9]).

2.2 Vesicular Glutamate Transporters

Experiments in rat brains have revealed that a subpopulation of specialized astrocytes expresses a distinct molecular signature resembling that of glutamatergic synapses and that release of glutamate from astrocytes occurs via vesicular glutamate transporter 1 (VGLUT1)-dependent exocytosis [14]. vGluT1-positive vesicles have been confirmed within astrocytic processes in the dentate-molecular layers, the stratum radiatum of the CA1 hippocampus, the frontal cortex, and the striatum of the rat, and in mice, when specifically examining the hippocampus [15]. Vesicle membrane-embedded VGLUT1 traffics in the secretory pathway of rat astrocytes (Fig. 2), slowly cycling between the plasma membrane and the cytoplasm; the mobility of these vesicles responds to a rise in cytosolic calcium, which renders their mobility more directional and triggers the release of glutamate [7]. The mobility of VGLUT1 depends on different types of cytoskeleton, as demonstrated by the disintegration of microtubules, actin filaments, or IFs ([7] and references within). VGLUT1 vesicles in astrocytes not only undergo exocytosis, but can also be recycled, forming a pool of vesicles distinct from early endosomes [16]. Trafficking of recycling VGLUT1 vesicles was further explored by examining the role of IFs, which abundantly interlink with microtubules and actin filaments. It was found that the expression of GFAP and vimentin (VIM), the two major IFs in postnatal astrocytes, affects the directionality of VGLUT1 recycling vesicles in response to increased concentrations of cytosolic calcium or ATP [16].

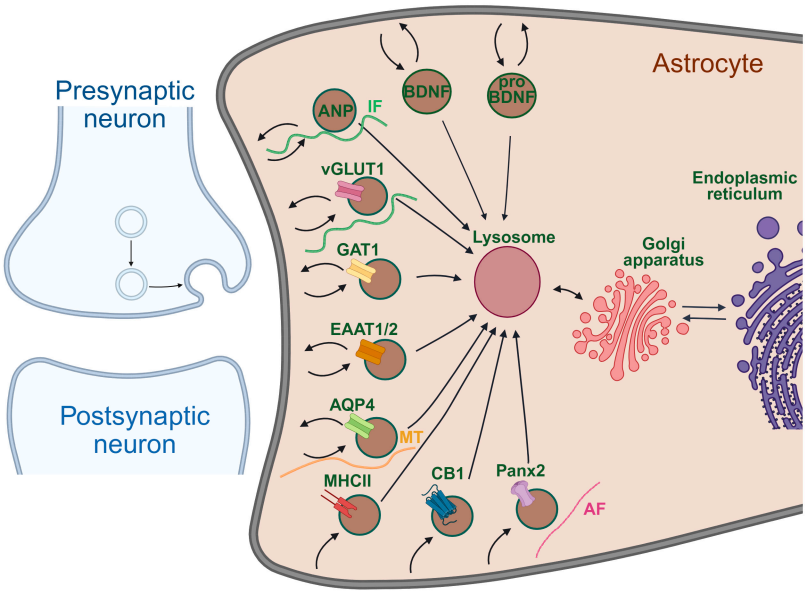

Figure 2: Schematic of vesicle endocytosis and recycling in astrocytes. Trafficking of endocytotic and recycling vesicles has been studied for: AQP4, aquaporin 4 water channel (regulating the abundance of plasma membrane isoforms of AQP4); EAAT1/2, excitatory amino acid transporter type 1 and 2 (glutamate (glu) uptake); GAT1, GABA transporter type 1 (uptake of GABA); vGLUT1, vesicular glutamate transporter 1 (uptake of glutamate into vesicles); ANP, atrial natriuretic peptide; proBDNF, brain-derived neurotrophic factor; BDNF, brain-derived neurotrophic factor (mature form); MHCII, major histocompatibility complex class II (presents processed antigens); CB1, Cannabinoid receptor type 1 (G-protein-coupled receptor (GPCRs) detecting endogenous and exogenous cannabinoids); Panx2, pannexin 2 (unclear role in astrocytes) In the case of vesicles containing ANP, vGLUT1, AQP4, and Panx2 trafficking of endocytic and recycling vesicles has been shown to depend on microtubules (MT), actin filaments (AF) and intermediate filaments (IFs), as shown in the schematic. Note that endocytosis of Panx2 was studied in the C6 glioblastoma cell line, not in primary astrocytes. Created in BioRender (https://BioRender.com/yf73ie3).

2.3 Transporters for GABA in the Plasma Membrane of Astrocytes

While glutamate is the major excitatory neurotransmitter, γ-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the CNS [17]. It plays essential roles in cognition, emotion, and behavior by regulating neuronal excitability and synaptic plasticity [17]. Termination of GABA action at the synapse occurs through its reuptake via plasma membrane-located GABA transporters (GATs) into nerve terminals and astrocytes [17]. Among the three main high-affinity GATs, GAT1 is expressed in neurons and astrocytes and is the predominant GABA transporter in the brain [18]. On the other hand, GAT3 is almost exclusively expressed in astrocytes [19]. The availability of GAT1 at the plasma membrane of rat astrocytes has been demonstrated to depend crucially on the recycling of GAT1 vesicles to the plasma membrane [20]. Trafficking of GAT3 vesicles has not been explored in murine astrocytes, but a study in *Drosophila* astrocyte-like glia reported that a calcium increase-triggered rapid Rab11-dependent internalization of GAT3 from the plasma membrane by endocytosis [21].

Vesicle transport of GATs mediates effective mechanisms of the GABA pathway, including synthesis, release, receptor-mediated transmission, reuptake, and catabolism that ensure proper GABAergic signaling and their malfunctions contribute to neurodevelopmental disorders, such as autism spectrum disorder and intellectual disability, and to psychiatric disorders, such as schizophrenia, bipolar disorder, and major depressive disorder [17].

Table 1: Vesicular localization of plasma membrane transporters, channels, and receptors in astrocytes.

Transporter/Channel/Receptor	Protein Function	Vesicular Process Studied	Ref.
EAAT1/GLAST	Uptake of glutamate from synaptic cleft	Exocytosis, Endocytosis, Recycling	[10]
EAAT2/GLT1	Uptake of glutamate from synaptic cleft	Exocytosis, Endocytosis, Recycling	[7]
VGLUT1	Uptake of glutamate from the cytosol into vesicles	Exocytosis, Endocytosis, Recycling	[7,16]
GAT1	Uptake of GABA from synaptic cleft	Endocytosis, Recycling	[20]
GAT3	Uptake of GABA from synaptic cleft	Endocytosis	[21]
Kir4.1 channel	Uptake of K^+ affecting uptake of glutamate	Exocytosis	[22,23]
Aquaporin 4 water channel	Transport of H_2O	Exocytosis, Endocytosis, Recycling	[24–26]
Pannexins	Panx1, ATP release Panx2, unclear	Exocytosis (Panx1), Endocytosis, Recycling (Panx2)	[27]
Cannabinoid receptor 1	Detecting endocannabinoids released from neurons, triggering astrocytic calcium signaling	Endocytosis	[28]

Note: EAAT1: Excitatory amino acid transporter 1; GLAST: Glutamate Aspartate transporter 1; EAAT2: Excitatory amino acid transporter 2; GLT1: Glial Glutamate Transporter 1; VGLUT1: Vesicular glutamate transporter 1; GABA: γ-aminobutyric acid; GAT1: GABA transporter type 3; GABA transporter type 1; GAT3: GABA transporter type 3; Kir4.1: Inwardly rectifying potassium (Kir) channel; Panx1: Pannexin 1; Panx2: Pannexin 2.

2.4 Kir4.1 Channel

Kir4.1 is an inwardly rectifying K^+ channel expressed exclusively in glial cells in the CNS [29]. It is highly expressed in astrocytes and participates in maintaining their resting membrane potential, regulating cell volume, and facilitating glutamate uptake [29]. During intense brain activity, extracellular potassium increases, and Kir4.1 in astrocytes is crucial for restoring healthy potassium levels. Failure to reduce extracellular potassium concentration to healthy levels can lead to overexcitation and seizures and contribute to depression [30]. A study on rat cortical astrocytes tracking the mobility of EGFP-tagged Kir4.1 revealed that at the vesicular level, Kir4.1 appears localized to the same vesicles that transport the aquaporin 4 water channel (AQP4) in the exocytotic pathway and is involved in regulated SNARE complex-dependent exocytosis [22]. In all Kir channels, the N-terminus of the proteins is required for post-Golgi trafficking to the plasma membrane [31]. High colocalization between Kir4.1 and AQP4 in the plasma membrane was anticipated, as both channels are anchored by the same dystroglycan complex [22]. On their way to the cell periphery, Kir4.1 vesicles travel predominantly along microtubules, although actin filaments are also involved in their mobility, but to a much lesser extent [22].

Kir4.1-laden vesicles in the cytoplasm of astrocytes respond to increased intracellular cAMP concentration with attenuated mobility by activating signaling pathways that enhance the activity of the enzyme glycogen synthase kinase-3 β (GSK3β), resulting in weakening the interaction between kinesins and vesicles [22]. In addition, prolonged elevations in cAMP may alter the expression of cytoskeleton-related genes, thus contributing to attenuated vesicle dynamics [22]. Nevertheless, both hypotheses remain to be tested. Reduced mobility of Kir4.1 vesicles after administration of (sub)anaesthetic doses of ketamine has also been suggested to be due to a cAMP-dependent mechanism, simultaneously reducing the surface density of Kir4.1 and inhibiting voltage-activated currents, affecting extracellular glutamate and K^+ homeostasis [22,23].

Dysregulation of Kir4.1 plasma membrane abundance and activity leads to altered neuronal activity, contributing to both chronic pain and several mental health disorders, as recently reviewed [32].

2.5 Aquaporin 4 Channel

AQP4 is the brain's predominant water channel and plays a crucial role in regulating water homeostasis in the CNS. It is expressed mainly in astrocyte endfeet that enwrap the blood-brain barrier and blood-cerebrospinal fluid interfaces [33]. It is encoded by a single gene; however, alternative splicing of *AQP4* produces several isoforms. In humans, two main canonical isoforms, M23 and M1, along with two extended isoforms (M23ex and M1ex), are expressed [33]. In the rat brain, there is an even greater variety of AQP4 isoforms, AQP4a-f, with AQP4a and AQP4c being analogues of M23 and M1, respectively [34]. Several AQP4 isoforms are located in the plasma membrane, predominantly aggregating into supramolecular structures known as orthogonal arrays of particles (OAPs), which are important for water permeability through the plasma membrane [33]. OAPs are a post-Golgi phenomenon, and their assembly requires plasma membrane-specific factors [26]. Specifically, AQP4a (M1), AQP4c (M23), AQP4e, and AQP4ex localize into OAPs, while the remaining isoforms are intracellular (AQP4b, AQP4d, AQP4f, AQP4-Δ4); most are predicted to play a role in the plasma membrane distribution of plasma membrane isoforms in murine and human astrocytes alike [25]. Trafficking of AQP4 vesicles in rat and mouse astrocytes has been investigated along the secretory pathway, in endosomes, and in lysosomes [24,35]. In rat astrocytes, trafficking of AQP4e-carrying vesicles has been shown to affect the abundance of AQP4 channels at the plasma membrane upon stimulation [24]. For example, AQP4 plasma membrane localization increases in conditions mimicking astrocyte reactivation and brain edema, attributed to rearrangements in actin and

VIM filaments accompanied by a transient change in vesicle mobility. Overexpression of AQP4e in rat astrocytes enhances the formation of OAPs, accelerating the kinetics of cell swelling and regulatory volume decrease, thereby displaying an active role for AQP4e in the regulation of water homeostasis in the rat brain [34]. Under physiological conditions, a portion of AQP4 continuously cycles between the cell surface and early and recycling endosomes, a process that depends on microtubules [36].

On the other hand, the rat intracellular AQP4 isoforms AQP4b and AQP4d never reach the plasma membrane, either in isosmotic conditions or in hypoosmotic conditions mimicking brain edema, and remain localized to early endosomes, late endosomes, lysosomes, and vesicles of the Golgi apparatus, as shown in primary rat astrocytes [25]. However, investigation of their role has revealed that they can reduce the density of OAPs, especially the AQP4d isoform, and thus affect astrocyte volume changes while remaining absent from OAPs [25]. Compared with AQP4b, AQP4d is particularly highly localized to early endosomes, which increases its trafficking in hypoosmotic conditions [25]. Similarly, the AQP4-Δ4 isoform in skeletal muscle is non-functional as a water channel, remains intracellular, and significantly reduces AQP4 cluster abundance at the plasma membrane. By accumulating newly synthesized channels in the ER, AQP4-Δ4 apparently alters the trafficking of plasma membrane AQP4 isoforms from the ER to the plasma membrane [37]. The mechanism by which AQP4d affects astrocyte volume regulation remains to be investigated.

Dystrophin protein has been proposed to affect AQP4 plasma membrane distribution [38], and it has recently been reported that the major cytolinker protein plectin plays an important role in anchoring AQP4 to the plasma membrane of astrocytes, supposedly via its linkage to actin and VIM filaments [8]. Possible direct interactions between AQP4, plectin, and the dystroglycan complex remain to be evaluated, but direct binding of plectin and the dystroglycan complex has been confirmed in other cell types [8]. The role of plectin in AQP4 vesicle mobility also remains unexplored; however, plectin has been shown to modulate the directional mobility of vesicles and mitochondria in neurons [8], thus, the impact of plectin on AQP4 vesicle mobility is anticipated. The observation that trafficking of several vesicle types is influenced by IFs is also important in the context of reactive astrogliosis, for example, after traumatic brain injury, which is often accompanied by edema [39]. In reactive astrocytes, the upregulation of IFs occurs alongside increased expression of plectin, which actively modulates general cytoskeletal reorganization and is also important for the positioning of AQP4 [8,35].

The mobility of AQP4-containing vesicles, affecting AQP4 surface expression, may be linked to pathological states in the brain. Recent studies reveal that AQP4 is important not only for maintaining brain water homeostasis in physiological and pathological conditions (e.g., after brain trauma), but also for enhancing the clearance of interstitial waste products in the brain by a glymphatic system. The glymphatic system uses interstitial fluid movement into the CSF and lymphatic system, thereby ensuring proper clearance mechanisms and preventing the accumulation of neurotoxic substances. The polarized presence of AQP4 in astrocyte endfeet, which is critically affected by the presence of extended AQP4 isoforms (AQP4ex) in the plasmalemma of astrocytes, enhances convective flow and thus contributes to solute clearance, such as amyloid-β (Aβ) in Alzheimer's disease [33]. Although these findings on AQP4 do not rule out other mechanisms of waste clearance, including passive diffusion, they may provide potential therapeutic targets for enhancing brain waste clearance [33]. The trafficking of AQP4 isoforms in astrocytes and their modulation have not been addressed yet.

2.6 Pannexins

Pannexins (Panx) are channel-forming glycoproteins. Panx1 and Panx2 are expressed in both astrocytes and neurons, with the latter being the largest of the three Panx proteins [40]. Pannexins expressed in different subcellular compartments likely exert distinct functional roles, particularly in the nervous system [27]. They mediate the extracellular release of signaling molecules, including ATP, with Panx1 being the main isoform for rapid ATP release [27]. After initial glycosylation in the ER and modifications in the Golgi apparatus, Panx1 is transported to the plasma membrane [41]. The functional role, intracellular localization, and trafficking of Panx2 in astrocytes remain unresolved. In the glioma C6 cell line, Panx2 did not appear colocalized with early endosomes and lysosomes, and its observed tumor-suppressive effects remain unexplored [42]. A recent study in zebrafish demonstrated that Panx2 is localized to ER-mitochondria contact sites and is involved in sensory perception and ocular health [43].

Although endogenous Panx1 and Panx2 were labeled in hippocampal neurons and astrocytes, showing non-overlapping signals, vesicular distribution in mammalian cells has so far been demonstrated only in the HeLa cell line, where the highest colocalization of Panx2 was observed with clathrin-coated vesicles, early endosomes, and recycling endosomes [27]. Panx2-containing vesicles were observed in close proximity to actin filaments, suggesting that this type of cytoskeleton might be the most important for their trafficking within the cell cytoplasm [27].

While Panx1 has many diverse roles in pathophysiology, including contributing to ischemic injury, inflammation, and seizure activity [44], the role of astrocytic Panx2 remains to be investigated. However, following an ischemic insult, the release of signaling molecules through Panx2 might affect the cellular metabolism and redox status of surrounding cells [45].

2.7 Cannabinoid Receptor 1

Cannabinoid type 1 (CB1) receptors are G-protein-coupled receptors (GPCRs) widely distributed in the brain. CB1 receptors are abundant at neuronal terminals, where their stimulation inhibits neurotransmitter release, and in astrocytes, where cannabinoid signaling is a key element of the tripartite synapse, playing important roles in the modulation of neuronal synaptic transmission and plasticity [46]. Endocannabinoids acting via CBs receptors trigger calcium signaling in astrocytes, resulting in the release of gliotransmitters such as glutamate, D-serine, and ATP, which modulate neuronal communication [47]. CB1 receptors in astrocytic plasma membrane are located close to synaptic terminals and vasculature, while subcellularly, mitochondrial type 1 cannabinoid receptors (mtCB1) have been found associated with mitochondrial membranes in astrocytes, affecting glucose metabolism, calcium signaling, and behavior [48–50]. Until recently, GPCR trafficking within astrocytes had not been investigated. The first such study involved monitoring the vesicle traffic of recombinant fluorescent protein chimeras of CB1, finding that in cultured rat visual cortex astrocytes, CB1 displayed a vesicular localization [28]. Similar to other vesicles in astrocytes [7], two populations of CB1 vesicles were described: relatively immobile, diffusible vesicles and mobile ones displaying properties of active transport along microtubules to/from the nuclear region [28]. In the rat visual cortex, CB1 vesicles were abundant in perinuclear regions of astrocytes and also further away from the nucleus, destined for delivery to the plasma membrane. The involvement of CB1 vesicles in constitutive endocytosis in astrocytes is anticipated but remains to be confirmed [28].

The involvement of CB1 in pathologies related to the role of astrocytes is a relatively recent field of research that addresses the role of astrocytic CB1 in mediating brain functions. In the context of pathologies, CB2 is expressed in solid astrocytomas and in healthy astrocytes. Its detection at low levels

in solid astrocytomas might be due to microglial/macrophage infiltration; however, this remains to be investigated [51].

3 Signaling Molecules Transported within Astrocytic Vesicles

3.1 Atrial Natriuretic Peptide

Membrane-bound vesicles in astrocytes also transport neuroactive peptides, which undergo exocytosis and influence astrocyte-to-neuron communication in the brain (Fig. 2, Table 2) [7]. Three types of natriuretic peptides have been identified in the brain: atrial natriuretic peptide (ANP), mainly synthesized by atrial myocytes; brain natriuretic peptide (BNP); and C-type natriuretic peptide (CNP). All act via ANP receptors expressed in astrocytes and neurons [52]. ANP is involved in regulating brain water and electrolyte homeostasis, local cerebral blood flow, and neuroendocrine functions [52]. The mobility of recycled ANP vesicles (those fused with and retrieved from the plasma membrane) in rat astrocytes decreases in response to elevated cytoplasmic calcium and ATP stimulation, similar to endo-lysosomal vesicles [16]. Moreover, both ANP and endo-lysosomal vesicles respond more weakly to these stimulations in the absence of IFs [16]. Thus, vesicle trafficking in astrocytes, affected by upregulation of IFs in reactive astrogliosis, can result in altered astrocyte-to-neuron communication but remains incompletely understood. Regarding other types of cytoskeleton, trafficking of ANP vesicles also depends on the dynamics of microtubules and actin filaments [7].

Trafficking of late endosomes and lysosomes in astrocytes also responds to stimulation with IFN-γ, which increases their movement speed [7]. The speed of late endosomes and lysosomes also depends on the expression of IFs; for example, in IFN-γ-treated IF-deficient astrocytes, they moved more slowly. As IFN-γ induces MHCII expression in late endosomes and lysosomes, the trafficking of these compartments to the plasma membrane of astrocytes may contribute to CNS inflammation [7].

Table 2: Vesicular cargo transported in astrocytic vesicles.

Peptide	Function	Vesicular Process Studied in Astrocytes	Ref.
ANP	Brain water and electrolyte homeostasis, local cerebral blood flow, and neuroendocrine functions	Endocytosis, Recycling	[7,16]
NPY	Role in neuroinflammation	Exocytosis	[53,54]
BDNF	Role in learning and memory	Endocytosis, Recycling	[55–57]
ATP	Role in synaptic plasticity	Exocytosis	[7]

Note: ANP: Atrial natriuretic peptide; NYP: Neuropeptide Y; BDNF: Brain-derived neurotrophic factor; ATP: Adenosine triphosphate.

3.2 Neuropeptide Y

Neuropeptide Y (NPY) is a highly conserved peptide that functions as a neurotransmitter. It is expressed in several tissues, with abundant expression in the brain, particularly in the amygdala, hippocampus, hypothalamus, and striatum [54]. The only published study addressing the trafficking of NPY in astrocytes revealed that NPY is present in dense core vesicles and is released via regulated exocytosis upon stimulation with glutamate [53]. *In vivo*, the trafficking of NPY dense core vesicles was examined in thalamocortical axons in the mouse cortex; NPY-tagged vesicles traveled preferentially in the anterograde direction and slowed their mobility in and near synapses [53,58]. Neuronal activity-dependent increases in intracellular calcium levels transiently enhanced the transport of preferentially anterograde NPY vesicles, similar to observations of VGLUT1 vesicles in astrocytes [58].

NPY in the brain is involved in attenuating neuroinflammation, which has important implications in the context of certain neurodegenerative diseases and during infections with pathogens, considering that astrocytes are important for immune functions of the CNS [1,54].

3.3 Brain-Derived Neurotrophic Factor

Brain-derived neurotrophic factor (BDNF) is synthesized primarily in neurons, from where it is released in pro-BDNF and mature BDNF forms. Astrocytes primarily take up pro-BDNF via the pan-neurotrophin receptor p75 through clathrin-mediated endocytosis [55]. Then, astrocytes can supply BDNF by recycling neuron-derived BDNF [55]. Endocytosis of extracellular mature BDNF occurs via the TrkB-T1 receptor into CD63-positive EVs, and its release from EVs is triggered by an increase in ATP [56]. BDNF recycling (resecretion of endocytosed BDNF) in astrocytes is mediated by an EV-dependent secretory pathway. Both uptake and resecretion of BDNF in astrocytes depend on vesicle-associated membrane protein 3, a key soluble NSF attachment protein receptor (SNARE) protein [57]. The release of BDNF from astrocytes has also been shown to depend on ketamine [59].

BDNF is one of the key neurotrophins in the brain and plays a crucial role in learning and memory [60]. By mediating the extracellular concentration of BDNF through uptake and recycling, vesicle trafficking in astrocytes contributes to BDNF-dependent synaptic functions.

3.4 ATP

The cross-talk between astrocytes and other cell types in the CNS is also coordinated by ATP [61]. The release of ATP from astrocytes is predominantly mediated by several plasma membrane proteins, such as connexin hemichannels, pannexins, volume-regulated anion channels, calcium homeostasis modulator protein 2 channels, and maxi-anion channels [61]. ATP release from astrocytes occurs either spontaneously, mainly in non-vesicular and calcium-independent ways, or from membrane-bound vesicles triggered by changes in calcium concentration [7,62].

ATP can be co-stored with peptides, as demonstrated for ANP vesicles in rat astrocytes [7]. These quinacrine dihydrochloride-labelled ATP vesicles responded to an increase in intracellular concentration of calcium by a decrease in their mobility and by exocytosis [7].

ATP is one of the major gliotransmitters and is considered essential for brain function, as impaired astrocytic ATP release leads to deficiencies in synaptic plasticity, depressive-like behavior, and sleep loss in rodents, as reviewed [61].

4 Pathogens Transported within Astrocytic Vesicles

Astrocytes are highly receptive cells for neurotropic pathogens. Their close contact with the endothelial cells of the BBB enables them to be among the first cells to take up pathogens, such as different neuroinvasive viruses that can penetrate through or between the endothelial cells of the BBB [1]. Viruses encountering the plasma membrane of astrocytes attach to various non-specific receptors [1]. Once bound, they are internalized into endocytic vesicles, allowing the viral genomic material to be released into the cytoplasm [63]. Such vesicles containing fluorescently labeled viruses can then be tracked upon entry into astrocytes.

4.1 Flaviviridae

The first study describing the mobility properties of fluorescently labeled flaviviruses in astrocytes reported the dynamic properties of vesicles containing internalized tick-borne encephalitis virus (TBEV), an important human pathogen [64]. It causes several thousand cases of meningitis, encephalitis, or

meningoencephalitis annually, resulting in 1–20% mortality, depending on the subtype, while in up to one-fifth of cases, patients are left with permanent neuropsychiatric disorders [64]. Once viral genetic material is released from endosomes, viruses can enter replication cycles and become neuroinvasive (neuroinvasiveness refers to the ability to infect and replicate in the nervous system). Astrocytes are potent producers of infectious viral particles, at levels several times higher than neurons [65]. For effective infection of host cells by viruses and for efficient release of mature viruses into the extracellular space, vesicle transport plays an important role.

For example, TBEV was found to be readily endocytosed into rat astrocytes, and the pool of vesicles with internalized TBEV showed two distinct mobilities: a non-directional one and a directional one, with directionality increasing over time post-infection [64]. Their movements indicated travel along actin filaments and microtubules, although actin filaments later became disintegrated, so trafficking in later stages of infection would rely on microtubules [64].

A subsequent study focused on the intracellular trafficking of another flavivirus in astrocytes, namely the Zika virus (ZIKV), which is associated with malformations of the fetal CNS in the form of microcephaly [65]. Several ZIKV strains, Brazil 2016 (ZIKV-BR), French Polynesia 2013 (ZIKV-FP), and Uganda #976 1947 (ZIKV-UG), again confirmed that astrocytes have a high capacity for viral production, surpassing neurons by several times in this ability [65]. Similar to TBEV, prolonged infection with strains ZIKV-BR and ZIKV-UG increased the trafficking speed of ZIKV vesicles, except for ZIKV-FP vesicles, for whose speed decreased [65]. The details of how different strains manipulate the trafficking machinery remain to be addressed and may involve differential expression of genes regulating intracellular vesicle-mediated transport, as observed in ZIKV-infected human peripheral neurons [66].

4.2 Polyomaviridae

Although in recent years most studies have addressed the infection of astrocytes by flaviviruses, the neuroscience community is increasingly aware that other viruses can also infect and replicate in astrocytes. However, the properties of viral trafficking upon cell entry and the potential for manipulating viral trafficking within cells remain largely unexplored. One example is JC polyomavirus (JCPyV), a human polyomavirus that establishes lifelong, asymptomatic, persistent infections in over half the world's population [67]. In immunosuppressed patients, JCPyV spreads to the CNS, where infection triggers progressive multifocal leukoencephalopathy, a rapidly progressing and debilitating demyelinating disease. The identified entry point into the CNS is the choroid plexus, whose epithelial cells are infected from peripheral tissue. From here, infection is disseminated via EVs containing JCPyV virions, which efficiently infect astrocytes by clathrin-dependent endocytosis and by micropinocytosis [68].

In contrast to viruses from the *Flaviviridae* family, viruses from the *Polyomaviridae* family are non-enveloped; however, they also enter cells via clathrin-dependent endocytosis and are immediately transported to early endosomes, as demonstrated in a human glial cell line [69]. Their sorting from endosomes to caveosomes, a neutral pH endocytic compartment, depends on Rab5-GTPase, which is also important for endosomal trafficking in astrocytes [7], as well as on cholesterol, caveolin-1, and pH [69]. Mutations in Rab5 have been shown to impair vesicle endosomal trafficking in astrocytes [7]. Modifications in endosomal uptake appear to reduce infection of cells in the CNS and once a selective Rab5 inhibitor is confirmed, there will be great potential for manipulating endosomal traffic and viral spread within the brain [70].

4.3 Herpesviridae

Viruses from the *Herpesviridae* family have also been shown to infect astrocytes. Herpes simplex virus type 1 (HSV-1) can cause life-threatening herpes simplex encephalitis by influencing the physiology of neurons and glial cells, including astrocytes [71]. HSV-1 infection of brain cortex cells induces differential expression of host proteins that regulate endosome trafficking [71]. Increased presence of heparan sulphate proteoglycans on the plasma membrane of HSV-1-infected astrocytes might enhance HSV-1 entry into astrocytes via endocytosis, as in the case of flaviviruses, although the trafficking of this virus remains to be studied in astrocytes [64].

5 Conclusions

Astrocytic vesicle trafficking along the cytoskeleton is a fundamental process essential for CNS function. By regulating extracellular levels of neurotransmitters, neuropeptides, and other signaling molecules, astrocytes rely on efficient vesicle trafficking to shape and sustain communication between glial cells and neurons. Its importance is further highlighted by studies showing that vesicle trafficking governs the delivery and retrieval of key transporters, channels, and receptors to precise locations within the plasma membrane. However, we still lack a detailed understanding of how cytoskeletal networks, including different types of filaments, their cytolinkers, regulatory proteins, and their interactions, shape intercellular signaling. In addition, changes in vesicle trafficking resulting from altered cytoskeletal architecture in different physiological and pathological states remain to be fully explored.

Advancing this field will not only clarify how astrocytes maintain CNS homeostasis but also reveal how disruptions in vesicle trafficking contribute to neurological and psychiatric disorders, opening new avenues for therapeutic intervention.

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Abbreviations

ATP	Adenosine triphosphate
Aβ	Amyloid-β
ANP	Atrial natriuretic peptide
AQP4	Aquaporin 4 water channel
AQP4ex	Extended isoform of AQP4

BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
BNP	Brain natriuretic peptide
cAMP	Cyclic adenosine monophosphate
CB1	Cannabinoid receptor type 1
mtCB1	Mitochondrial cannabinoid receptor type 1
CNP	C-type natriuretic peptide
CNS	Central nervous system
EAAT1	Excitatory amino acid transporter 1
EAAT2	Excitatory amino acid transporter 2
EGFP	Enhanced green fluorescent protein
ER	Endoplasmic reticulum
EV	Extracellular vesicle
GABA	γ-aminobutyric acid
GAT1	GABA transporter type 1
GAT3	GABA transporter type 3
GDI	GDP dissociation inhibitor
GFAP	GFAP
GLAST1	Glutamate Aspartate transporter 1
GLT1	Glial Glutamate Transporter 1
GPCR	G-protein-coupled receptor
GSK3β	Glycogen synthase kinase-3 β
GDP	Guanosine diphosphate
GTP	Guanosine triphosphate
HSV-1	Herpes simplex virus type
IF	Intermediate filament
IFN-γ	Interferon gamma
JCPyV	JC polyomavirus
Kir	Inwardly rectifying potassium (Kir) channel
MHCII	Major histocompatibility complex class II
mtCB1	Mitochondrial CB1 receptor
NPY	Neuropeptide Y
Panx	Pannexins
Rab	RAB GTPase
SLC1	Solute carrier 1
SNARE	Soluble NSF attachment protein receptor
TBEV	Tick-born encephalitis virus
VGLUT1	Vesicular glutamate transporter 1
VIM	Vimentin
ZIKV	Zika virus

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