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Review

New insights in endosomal dynamics and AMPA receptor trafficking

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ABSTRACT

The trafficking mechanisms that control the density of synaptic AMPA-type glutamate receptors have received significant attention because of their importance for regulating excitatory synaptic transmission and synaptic plasticity in the hippocampus. AMPA receptors are synthesized in the neuronal cell body and reach their postsynaptic targets after a complex journey involving multiple transport steps along different cytoskeleton structures and through various stages of the endocytic pathway. Dendritic spines are important sites for AMPA receptor trafficking and contain the basic components of endosomal recycling. On induction of synaptic plasticity, internalized AMPA receptors undergo endosomal sorting and cycle through early endosomes and recycling endosomes back to the plasma membrane (model for long-term potentiation) or target for degradation to the lysosomes (model for long-term depression). Exciting new studies now provide insight in actin-mediated processes that controls endosomal tubule formation and receptor sorting. This review describes the path of AMPA receptor internalization up to sites of recycling and summarizes recent studies on actin-mediated endosomal receptor sorting.

Contents

1. Introduction

At excitatory synapses, activation of glutamate receptors provides the primary depolarization signal in excitatory neurotransmission. Most excitatory transmission in the brain is mediated by AMPA-type ionotropic glutamate receptors [1–3]. AMPA receptors have a major influence in the strength of the synaptic response and are crucially involved in synaptic plasticity and learning and memory processes [4–6]. Bidirectional regulation of synaptic AMPA receptor number and function at synapses underlies two of the most well studied examples of synaptic plasticity in the brain, long-term potentiation (LTP) and long-term depression (LTD) [6–8]. The last decade, several studies have provided strong evidence that controlling AMPA receptor density at individual synaptic sites is central to modifications in synaptic strength and plasticity [9,10]. There are now several lines of evidence that AMPA receptor density is carefully regulated by basic cellular trafficking mechanisms, such as

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Golgi-derived secretory transport, receptor exocytosis, lateral diffusion, endosomal recycling, and receptor degradation [5,7,11–14]. Thus, understanding the mechanisms by which AMPA receptors travel to and from synapses is a major challenge in basic neuroscience research and of fundamental importance to understand the molecular basis of synaptic plasticity and learning and memory processes in the brain.

The number of AMPA receptors available to synapses is regulated by the endocytosis and exocytosis (recycling) of receptors locally at synapses [6,15]. Like any other internalized membrane protein endocytosed AMPA receptors undergo endosomal sorting, which subsequently targets them for degradation to the lysosomes (model for LTD) or recycling back to the surface membrane (model for LTP) [6,7,16]. Dendritic spines are important sites for postsynaptic receptor internalization and contain the basic components of the endocytic machinery. AMPA receptor endocytosis occurs through a clathrin- and dynamin-dependent pathway [17,18], while small Rab GTPases and their effectors regulate further endosomal trafficking. The classic endosomal Rab proteins, Rab5, Rab4 and Rab11 have all been implicated in endosomal receptor and membrane trafficking in dendrites. Rab5 controls transport to early endosomes (also called sorting endosomes) whereas Rab4 and Rab11 are involved in the regulation of endosomal recycling back to the plasma membrane. The communication and transport between sequentially organized Rab domains most likely control endo- and exocytic recycling of AMPA receptors [9,10,19,20]. Once exocytosed onto the surface of the dendritic shaft or spine, AMPA receptors diffuse laterally into the postsynaptic density [21,22] where they are transiently immobilized by interactions with postsynaptic scaffolding proteins [23]. Recent evidence indicates that actin-mediated myosin motor protein transport regulates local AMPA receptor turnover at synapses [24–26]. However, a series of additional papers established that the association of actin on early endosomes has implications for novel functions of F-actin that go well beyond a direct role in navigating local AMPA receptor trafficking at the synapse. Here, data suggest that actin works together with the endosomal machinery and controls the mechanical force to drive membrane invagination [27] and regulates specialized receptor sorting [28].

This review will first summarize the current knowledge of the trafficking pathways that guide AMPA receptors along the endocytic route. We focus on actin-mediated regulatory steps that contribute to receptor internalization and endosomal sorting in non-neuronal cells and look for the connection with AMPA receptor trafficking.

2. Structure and function of AMPA receptors

AMPA receptors are composed of four closely related subunits GluA1-4 (also named GluR1-4 or GluRA-D), which combine to form tetrameric ion channels [2,3]. Most AMPA receptors are heterotetrameric, they assemble from four subunits, consisting of symmetric 'dimer of dimers' of GluA2 and either GluA1, GluA3 or GluA4 in various stoichiometries [29]. In the mature hippocampus, most AMPA receptors are composed of GluA1/2 or GluA2/3 combinations, whereas GluA4-containing AMPA receptors are expressed mainly in early postnatal development. The oligomeric combinations are formed in the endoplasmic reticulum (ER), possibly assembling as dimers of dimers [14]. The AMPA receptor GluA2 tetramer has recently been crystallized [30]. Like all other ionotrophic glutamate receptors, AMPA receptors are comprised of four domains—the extracellular N-terminal domain (NTD) and the ligand-binding domain (LBD), the membrane-embedded ion-channel, composed of three transmembrane segments and a re-entrant pore loop and an intracellular C-terminus. The extracellular and transmembrane regions of AMPA receptor subunits are very similar but vary in their intracellular cytoplasmic tails. Specific proteins that bind to the cytoplasmic tails of GluA subunits are implicated in the exocytosis and endocytosis of AMPA receptors [31–33].

3. AMPA receptor internalization

Several studies showed that AMPA receptor internalization in an activity-dependent manner along the endocytic pathway leads to LTD. Stimulation of excitatory synapses with glutamate – by means of global AMPA, NMDA or insulin treatment – enhances AMPA receptor internalization through clathrin-mediated endocytosis in cultured neurons [32,34]. Endocytic removal of AMPA receptors occurs mostly from extrasynaptic sites [35]. This observation is consistent with the localization of stable, long-lasting sites of endocytosis on dendritic spines lateral to the PSD, named endocytic zones (EZ), where endocytosis of other postsynaptic receptors occurs [36]. Several endocytic proteins including clathrin, AP-2, and dynamin have also been found localized lateral to PSD by immunogold electron microscopy, suggesting that lateral domains of the spine membrane organize endocytic protein machinery [37]. The EZ is linked to the PSD via the interaction between dynamin-3 and the postsynaptic adaptor Homer [38]. Disruption of dynamin-3 or its interaction with Homer uncouples the PSD from the EZ, resulting in synapses lacking postsynaptic clathrin. Loss of the EZ leads to a loss of synaptic AMPA receptors and reduced excitatory synaptic transmission that corresponds with impaired synaptic recycling.

The mechanism of clathrin-mediated AMPA receptor internalization is well investigated. Functional studies of the early endosome-associated small GTPase Rab5 showed that it is localized close to the PSD and facilitates AMPA receptor internalization in response to LTD-inducing stimuli [39]. Moreover, direct binding of the GluA2 cytoplasmic tail to the clathrin adaptor complex AP-2 is required for NMDA-induced AMPA receptor endocytosis and essential for LTD [40]. Consistently, internalized AMPA receptors colocalize with AP-2 [41] and an integral component of clathrin-coated pits, Eps15 [18]. The AP-2/GluA2 interaction occurs via binding of the μ2-adaptin subunit of AP2 to basic residues in the GluA2 carboxy terminal tail [42]. It is likely that NMDA-induced phosphorylation changes promote the association of AP-2 with within GluA and lead to the accumulation of AMPA receptors in clathrin/AP-2-coated pits. Other mechanisms, including phosphorylation or ubiquitination of GluA C-terminal tails, phosphatidylinositol signaling and the association with Huntingtin interacting protein 1 (HIP1) are likely to contribute to the AMPA receptor internalization [43–47]. Of great interest are the recent data showing that ubiquitination of GluA1-containing AMPA receptors by the specific E3 ligase, Nedd4-1 (neural-precursor cell-expressed developmentally downregulated gene 4-1) mediates the internalization of surface AMPA receptors and their trafficking to the lysosome [48,49]. Consistently, glutamate receptors in nematodes are subject to multi-ubiquitination, which targets receptors for internalization and late endosomal/lysosomal degradation [50].

4. AMPA receptor sorting and recycling

Receptor internalization is caused by different signaling pathways and AMPA receptors are differentially sorted between recycling and degradative pathways following endocytosis, depending on the endocytic stimulus [51]. For example, while AMPA receptors internalized in response to AMPA stimulation are trafficked to dendritic lysosomes and degraded, receptors internalized in response to NMDA activation are sorted into recycling endosomes in a PKA-dependent manner. It was also found that the AMPA

receptor subunits are differentially sorted along the endosomal pathways [52]. After AMPA-induced internalization, homomeric GluA2 enters the recycling pathway, but following NMDA stimulation, GluA2 is diverted to late endosomes/lysosomes. In contrast, GluA1 remains in the recycling pathway, and GluA3 is targeted to lysosomes regardless of NMDA receptor activation. These data suggest that GluA2 is dominant over GluA1 to determine sorting of internalized receptors.

The intracellular C-terminal domain of AMPA receptors makes direct contact with various components of the postsynaptic density and is responsible for receptor endocytosis [31,33]. The last few amino-acids in the carboxyl termini (also named type II PDZ-binding motifs) of AMPA receptor subunits GluA2 and GluA3 have been shown to bind to several synaptic PDZ domain-containing proteins (named after the proteins in which the PDZ sequence motifs were originally identified; PSD-95, discs large, zona occludens-1). Several lines of evidence indicate that the PDZ-based interactions of GluA2/3 are important for the synaptic targeting, clustering and internalization of AMPA receptors. For example, a peptide containing the GluA2 PDZ binding motif disperses GluA2 clusters [53] and mutations of the GluA2 PDZ binding site that selectively block GluA2 binding to PDZ proteins accelerate GluA2 endocytosis at synapses [54].

GluA2/3 mainly interact with the type II PDZ-proteins such as the glutamate receptor-interacting protein/AMPA receptor-binding protein (GRIP/ABP; encoded by two distinct genes, GRIP1 and ABP/GRIP2) and protein interacting with C kinase 1 (PICK1) [6,7,54–56]. While the precise role of these PDZ proteins in AMPA receptor endosomal recycling remains unclear, the balance between GRIP/ABP and PICK1 interactions with GluA2 after PKC phosphorylation seems to be a critical factor [57–59]. In hippocampal and parallel fiber-Purkinje cell synapses, PICK1 appears to drive the synaptic removal of phosphorylated GluA2 receptors [57,60,61]. A popular model holds that binding of PICK1 together with associated protein kinase C (PKC), and release of GRIP/ABP binding, leads to receptor detachment from the PSD scaffold by phosphorylation of serine 880 [62–64]. In this way, GRIP/ABP may play a role in stabilizing the pool of AMPA receptors at the synaptic plasma membrane [62]. However, a significant portion of GRIP/ABP is also detected on internal compartments [53,65–67], and differential palmitoylation distinguishes the intracellular GRIP/ABP from plasma membrane-associated GRIP/ABP. Recent data from the Henley lab suggest that overexpression of palmitoylated GRIP1 enhances, and unpalmitoylated GRIP1 inhibits NMDA-induced AMPAR internalization [68]. Thus, instead of exerting their effects at the synapse, it is likely that GRIP/ABP predominantly acts on the intracellular reserve pool of receptors, presumably in the endosomal system. These data are consistent with other reports showing that GRIP1 associates with the early endosomal protein NEEP21 (neuron-enriched endosomal protein of 21 kDa) to stimulate AMPA trafficking to the recycling pathway [69,70]. Down-regulation of NEEP21 perturbs AMPA receptor recycling and abolishes stable induction of LTP [71]. Interestingly, NEEP21 also interacts with the endosomal SNARE proteins syntaxin 13 [69].

5. Actin and receptor endocytosis

The importance of the actin cytoskeleton and actin-based motor protein myosin-V trafficking for local AMPA receptor recycling has also recently been demonstrated [26,72]. These studies not only showed that actin-dependent transport pathways are important for AMPA receptor endosome trafficking but also revealed that myosin-Vb is a "Ca^{2+} sensor" for synaptic receptor targeting [26]. The Ehlers lab demonstrated that under high Ca^{2+} concentrations myosin-V undergoes a conformational change that allows for binding to Rab11-family interacting protein 2 (Rab11-FIP2) adaptors on Rab11 positive recycling endosomes. The association of myosin-Vb with Rab11-FIP2 moves AMPA receptor containing recycling endosomes into spines and increases their surface expression. Consistent with this model, acutely blockage of myosin-Vb activity in a transgenic model impairs LTP [26]. These data demonstrate that the Ca^{2+} dependent synaptic AMPA receptor insertions could be mediated by directional transport along the actin cytoskeleton. In addition, to the role of actin in intracellular receptor transport, actin polymerization on a membrane surface has long been known to generate sufficient mechanical force to drive membrane invagination and receptor internalization [27]. Indeed the ability of actin to form tubules at the plasma membrane and the trans Golgi network (TGN) has been firmly established [73–75]. Exciting new information now provides insight in the actin machinery that together with Arp2/3 generates tubules on endosomes (Fig. 1).

The Arp2/3 multiprotein complex is a key factor in branching actin from pre-existing filaments and thereby controls membrane dynamics and organelle remodeling [76]. Arp2/3 is concentrated in the spine [37] and is regulated by nucleation promoting factors (NPFs) of the WASP family, which includes cortactin, WAVE/SCAR and N-WASP that are all known to be important for spine formation and plasticity [77]. Two additional NPFs, WHAMM, and WASH were recently discovered [78–80], that extend the repertoire of functions assigned to the classical NPFs. We here focus on WASH, because it localizes to the endosomal system, while WHAMM is associated with the Golgi complex [78]. WASH functions in the cell within a 500–550 kDa multiprotein complex that controls the activity of WASH towards Arp2/3 and fission of early endosomal tubules [80,81]. The core of the complex is constituted by FAM21, Strumpellin, KIAA1033, CCDC53, while subunits of actin capping protein are peripherally associated. Interestingly, Strumpellin mutations are associated with the human neurodegenerative disorder hereditary spastic paraplegia [82], suggesting that abnormalities of actin dynamics on endosomes play a role in the disease.

The domain architecture of WASH reveals a sequential organization into four non-overlapping regions with distinct functions (Fig. 1). The N-terminus is required for association of WASH with the endosomal membrane through association with FAM21 [79]. This is followed by a region with affinity for tubulin and likely involved in microtubule interactions, a proline rich domain binding SH3 proteins, and a C-terminal VCA region important for actin and Arp2/3 complex binding. WASH is heterogeneously distributed within the endosomal network. WASH is concentrated in patches enriched for recycling markers Rab4 and Rab11, and to a lesser extent with Rab5 and Rab7 endosomes. Depletion of WASH by siRNA sprouts transferring-containing tubules from endosomes which is phenocopied by pharmacological inhibition of dynamin. Possibly WASH and dynamin act in a same pathway, a notion that is supported by the finding that WASH and dynamin co-immunoprecipitate. These observations are reminiscent of N-WASP function in clathrin mediated endocytosis, where a burst of N-WASP induced actin polymerization is required for the dynamin-dependent fission of tubules at the plasma membrane [75]. WASH–Arp2/3 complex controlled actin polymerization could generate a pushing force that counteracts pulling provided by endosome-associated microtubule motors. The outcome of which is increased tension that could support dynamin mediated fission of transport carriers from sorting and recycling endosomes. Interestingly, the WASH complex was independently discovered in a search for interacting proteins of the retromer vps subcomplex [83]. This so called cargo recognition complex together with a sorting nexin structural dimer constitutes retromer that sorts transmembrane proteins into tubules for retrieval from endosomes to the TGN [84]. Unlike knock down of vps26, silencing WASH complex com-

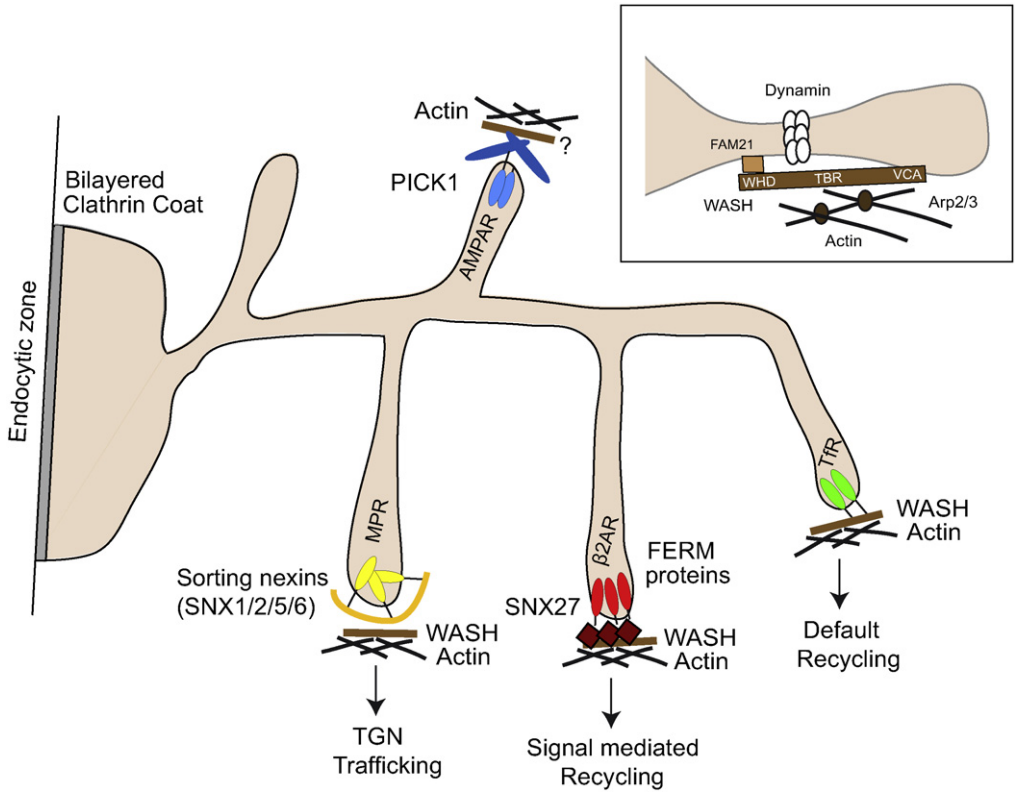

Fig. 1. Model for the organization of actin-dependent sorting events in the endosomal system. A tubular endosomal network with distinct exit sites for default recycling cargo (TfR), for AMPA receptors, for sorting signal mediated recycling of β2-AR to the plasma membrane, and for returning receptors via the retromer complex to the trans Golgi network. Signal mediated recycling of β2-AR involves SNX-27 that might tether β2-AR containing tubules via FERM proteins to F-actin. WASH is associated with each of these tubules, and further work is needed to understand precisely if and how the WASH complex contributes to tubular endosomal membrane remodeling and perhaps incoporation of coorporation of cargo molecules. PICK1 is a negative regulator of Arp2/3 and involved in NMDA-induced AMPA receptor internalization. Inset shows the domain architecture of WASH and how WASH might work in the endosomal system. The N-terminal WHD domain is recruited to the endosomal membrane via other components of the WASH complex, such as FAM21. The tubulin binding region (TBR) of WASH could interact with microtubules while the C-terminal VCA domain recruits actin and activates Arp2/3 complex. The newly formed actin filaments can recruit additional factors for membrane deformation and subsequent scission of carriers. Possibly WASH and dynamin act in a same pathway. *Abbreviations:* MPR; mannose 6-phosphate receptors, AMPAR; (-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, β2-AR; β2-adrenergic receptors, TfR; transferrin receptor.

ponents does not affect the endosome to TGN pathway, although the length of endosomal tubules was increased. Conversely, the vp26–vps35–vps29 complex is essential for WASH localization to the endosomal membrane, suggesting that it serves as a hub for recruiting proteins to endosomes or regulation of membrane tubule dynamics.

While a definitive role of WASH in neurons remains to be established, we suspect that it might provide a key control function in endosomal receptor trafficking pathways within dendritic spines. It could do so in conjunction with PICK1, a PDZ-BAR-domain protein that can be recruited to endosomes [85]. PICK1 is a negative regulator of Arp2/3 and involved in NMDA-induced AMPA receptor internalization [86,87]. Conceivably, the balance between the opposing effects of WASH and PICK1 on Arp2/3 might serve as a powerful mechanism to coordinate actin dynamics and AMPA receptor endocytosis (Fig. 1).

6. Actin microdomains in endosomal recycling routes

Recycling from endosomes is a very efficient process for returning proteins to the plasma membrane and for a long time was considered to be a signal independent bulk flow event [88]. Sorting of membrane proteins into thin endosomal tubules with a high surface to volume ratio creates the geometric conditions for their segregation from soluble proteins [89]. After scission, the tubulovesiciular carriers ultimately fuse with the plasma membrane. Over the years it has become clear that recycling signaling receptors in particular, deviate from the default-recycling pathway. Instead they reach the plasma membrane via differently regulated and signal-dependent mechanisms, reflecting the requirements of their specific downstream signaling pathways [90]. A repertoire of mechanistically distinct recycling pathways [91], just like the various endocytic internalization routes [92], contributes to the generation of specific, and versatile cellular responses.

Perhaps the first indication for the existence of alternative recycling pathways was the original discovery of von Zastrow's lab that agonist induced β2-adrenoreceptor (β2-AR) recycling requires a PDZ recognition motif in its C-terminal cytoplasmic tail. Phosphorylation or disruption of this sequence by a single point mutation targets the receptor for degradation [93] (Fig. 1). High-resolution live imaging showed that internalized β2-AR enters endosomes, the receptor then concentrates in Rab4 and Rab11 positive tubules that bud off β2-AR carriers for return to the plasma membrane [28]. Importantly β2-AR tubules are not enriched in the bulk recycling marker Transferrin receptor (TfR) (Fig. 1) and are devoid of the delta opoid receptor which is targeted into the degradative pathway [94], suggestive of an active principle for selective incorporation of β2-AR in a specific recycling domain. Since the β2-AR tubules are decorated with rapidly turning-over F-actin, Arp2/3, and a subunit of the WASH complex, it is a distinct possibility that the dynamic assembly of actin at this location is under control of the WASH complex. β2-AR localizes to one only out of every four TfR-containing endosomal tubules. Precisely these tubules are more stable than the other population of highly dynamic TfR tubules that is devoid

of β2-AR and also does not contain cortactin. β2-AR diffuse considerably slower than TfR into the tubules, which together with selective stabilization of these recycling tubules makes a strong case for a role of actin in the sequence-specific sorting of β2-AR. Indeed, actin depolymerization or knock-down of cortactin selectively impairs concentration of β2-AR in tubules and β2-AR recycling. The requirement for β2-AR to be sorted in these tubules is encapsulated within the PDZ binding domain. This sequence motif is also sufficient because it can be transplanted onto the delta opoid receptor, which is then diverted from the degradative pathway into the β2-AR endosomal recycling tubules. β2-AR interacts with NHERF1/EBP50 [95], a EBP50–ezrin complex could therefore serve as molecular link between β2-AR in endosomal recycling tubules and F-actin [96].

A combined knock-down of NHERFs however marginally impacts on β2-AR recycling [97] making this a less likely scenario. Instead an interaction between β2-AR and the PDZ domain of Sorting Nexin 27 (SNX27) on endosomes appears to be required for recycling of β2-AR [97]. SNX27 localizes to sorting endosomes/recycling endosomes and has been implicated in the regulation of endocytic recycling in CD4-positive T cells [98]. This atypical sorting nexin contains a PI(3)P binding PX domain and an N-terminal PDZ domain, with similarity to the PDZ domain of the NHERFs. It is at this moment not known if the requirement for the interaction with SNX27 is related to actin-dependent sorting of β2-AR into the endosomal recycling tubules [28]. Such a mechanism invokes some sort of interaction between SNX27 and F actin, which could be provided for by the presence of a FERM domain in its C-terminus [99]. Alternative support derives from studies on the regulation of NADPH oxidase component p40(phox) in superoxide production. Interestingly the PX domain of p40phox binds to moesin [100] and actin [101]. Thus some PX domains not only interact with phosphatidylinositols, but can also use distinct mechanisms for binding to actin. Other membrane proteins including 5-HT4a receptor [102], NMDA receptor 2C [103], and the G protein-gated K3 potassium channel [104] associate via a PDZ domain interaction with SNX27 which regulates their intracellular trafficking. More refined studies are necessary to pinpoint the precise locus of SNX27 function. These will likely establish whether SNX27 function in endosome recycling represents a novel general mechanism, or an adaptation of the role of PDZ domains in protein sorting [105]. At the moment it remains unclear whether AMPA receptor endocytosis is regulated by SNX27 or other PX and PDZ domain containing proteins. However, from these experiments it seems very likely that actin and PDZ domain containing proteins co-regulate endocytic recycling pathways.

7. Conclusion

It has intrigued scientists for a long time how receptors can be internalized and targeted for degradation or recycling back to the cell surface. The last few years, the field of AMPA receptor trafficking is moving forward at fast speed. New proteins interacting with AMPA receptors or with the neuronal endocytic machinery are constantly being identified. Neuronal pathways are discovered where AMPA receptors are assembled, sorted and targeted [106]. We are starting to identify the core machinery AMPA receptor endocytosis along actin structures, as well as the regulatory mechanisms that coordinate their dynamic behavior close to the EZ, such as lateral diffusion [25] and receptor recycling [26,38,72]. Much remains unclear about the regulation of the receptor trafficking machinery during synaptic plasticity. Is the actin-mediated endocytosis linked to the signal transduction pathways triggered by NMDA or AMPA receptor activation? Are other cytoskeletal elements, such as microtubules involved? Recent progress described that vacuolar endosomes are connected to a vast network of tubules and began to unravel the players regulating actin dynamics in the endosomal system (Fig. 1). Although most of these studies are performed in other model systems, future research in this promising area will help us to precisely dissect the importance of the various actin-based mechanisms during AMPA receptor endocytosis.

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