Dendritic Organelles for Postsynaptic Trafficking

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Abstract. The development, maintenance, and plasticity of synapses require the trafficking of molecular components to postsynaptic specializations distributed across elaborate dendritic arbors. The large size and geometric complexity of dendrites necessitate specialized mechanisms that can both deliver postsynaptic cargo over extended distances and regulate dendritic composition on a submicron scale. Despite the fundamental importance of membrane trafficking in neuronal development and synaptic plasticity, the cellular rules governing postsynaptic trafficking are only now emerging. We review here current knowledge on the organization of dendritic organelles, and describe cell biological mechanisms that allow long-range transport of postsynaptic components that are then locally processed at individual synapses.

1 Introduction

With long and highly branched processes extending up to several hundred microns from the cell body, neurons have surface areas up to 10,000 times greater than typical mammalian cells and display a remarkable degree of locally specified physiological properties (106). These spatially restricted properties (e.g. action potential generation and neurotransmitter release in the axon, postsynaptic response to neurotransmitters in dendrites, synapse-specific modification for long-lasting plasticity) are due to a high degree of molecular compartmentalization, the basis for which is only now emerging.

While inhibitory synapses are typically localized on the dendritic shaft (190), most excitatory synapses in the brain are localized on micron-sized membranous protrusions present along the entire length of dendrites (85). These dendritic spines contact one or more presynaptic terminals, and the sites of contact contain a dense array of receptors, scaffold proteins, and signaling molecules at the postsynaptic density (PSD) (96). The molecular content of dendritic branches, individual spines, and the PSD is subject to rapid and long-lasting modification based on developmental stage and patterns of neural activity (45, 122, 290). This multi-layered compartmental organization requires long-range transport of postsynaptic proteins to reach the most

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distal dendrites through geometrically complex branches. Once delivered to spines, synaptic components including postsynaptic receptors are subject to local trafficking rules, which determine whether they are incorporated into synapses or removed from the plasma membrane, and whether they are recycled or degraded.

Many aspects of postsynaptic receptor trafficking are regulated by neuronal activity, allowing rapid changes of receptor amount at the postsynapse and thereby the strength of postsynaptic responses (24). Dendritic membrane protein trafficking has emerged as a key postsynaptic mechanism underlying synapse development and various forms of synaptic plasticity, such as long term potentiation (LTP) and depression (LTD) (45). Because individual PSDs contain only tens to a few hundred neurotransmitter receptors, the addition or subtraction of just a few molecules can alter neurotransmission (39, 182, 189, 277). Moreover, adjacent dendritic spines can have strikingly different steady-state levels of synaptic proteins (13, 64, 183), implying that postsynaptic trafficking is subject to stringent spatial regulation.

In the present chapter, we describe the fundamental organization of neuronal organelles, emphasizing that, while many basic principles established in model systems such as yeast and fibroblasts also apply to neurons, neurons have many of their own rules to orchestrate protein trafficking. Our discussion will be limited largely to protein trafficking in dendrites. After presenting formal principles of protein trafficking in dendrites, we review recent data explaining how specific mechanisms known to control the dynamics of postsynaptic components can be integrated in a larger perspective taking into account specific properties of neuronal organelles. Due to limitations of space, local mRNA translation in dendrites, which is an important aspect of synaptic function and plasticity (272, 274), will not be reviewed here.

2 Dendritic Organelles

2.1 ER, Golgi and the Neuronal Secretory Pathway

2.1.1 Fundamental Organization of the Secretory Pathway

Maintenance of the dendritic membrane requires continuous delivery of newly synthesized membrane proteins through the secretory pathway. The secretory pathway consists of an organized array of membrane bound organelles and tubulo-vesicular intermediates that are required for the synthesis, maturation and transport of proteins destined for the cell surface (210). The main organelles of the secretory pathway are the endoplasmic reticulum (ER), the ER-Golgi intermediate compartment (ERGIC), the Golgi apparatus (GA) and the trans-Golgi-network (TGN) (Fig. 1) (163). Newly synthesized proteins typically pass through these organelles in a sequential manner, with transport between compartments mediated by vesicular carriers moving along microtubules (163). The machinery for eukaryotic secretory trafficking has been largely conserved during evolution, and many of the basic principles first established in yeast apply to higher eukaryotic cells including neurons (107, 157).

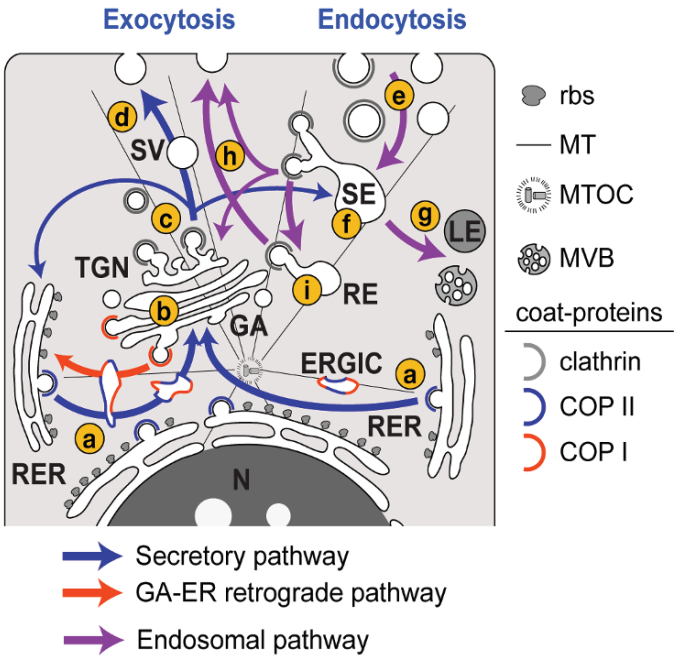

Fig. 1. Membrane trafficking pathways in eukaryotic cells. *Secretory pathway*. Newly synthesized membrane proteins exit the endoplasmic reticulum (ER) in COP-II-coated vesicles (**a**), which form at specialized locations termed ER-exit sites (ERES). Cargo is then trafficked to the Golgi apparatus (GA) for post-translational modifications (**b**) via ER-Golgi intermediate compartments (ERGIC). ER-resident proteins are retrieved from the ERGIC or GA and trafficked back to the ER in COP-I coated-vesicles. Cargo progresses through the GA is sorted at the TGN (**c**), and trafficked either directly or via endosomes to the plasma membrane for exocytosis (**d**). *Endosomal pathway*. Membrane proteins are internalized by means of clathrin-dependent or clathrin-independent endocytosis (**e**). Newly internalized vesicles fuse to form early/sorting endosomes (SE) where cargo is sorted (**f**) and trafficked to late endosomes/multivesicular bodies (MVBs) for degradation (**g**), to the TGN, or back to the plasma membrane (**h**), either directly or via recycling endosomes (**i**). *Abbreviations*. N, nucleus; RER, rough endoplasmic reticulum; ERGIC, endoplasmic reticulum-Golgi intermediate compartment; GA, Golgi apparatus; TGN, trans-Golgi network; SV, secretory vesicle; SE, sorting endosome; LE, late endosome; RE, recycling endosome; rbs, ribosome; MT, microtubule; MTOC, microtubule organizing center; MVB, multivesicular body.

While nuclear and cytoplasmic proteins are synthesized in the cytoplasm, the secretory pathway is the obligatory biosynthetic pathway for most surface and extracellular proteins, as well as for transmembrane and intraluminal proteins destined for all membrane bound organelles other than mitochondria, chloroplasts and peroxisomes (157, 163). The entry of proteins into the secretory pathway is coupled to their synthesis and occurs at the rough ER (RER) where actively translating ribosome-mRNA complexes associate with the ER membrane (246). Ribosomes are targeted to the ER via the signal peptide recognition particle (SRP) which associates with the translocon, the protein channel complex through which nascent

polypeptides are translocated across the ER membrane (132, 246). Ribosomes are released as protein elongation stops and polypeptides then adopt their proper three-dimensional structure in the ER lumen, assisted by chaperone proteins such as BiP, calnexin, and calreticulin (144). Protein folding in the ER is coupled to post-translational modifications, including N-glycosylation and disulfide bond formation. Proper folding and maturation of proteins in the ER is essential for their secretory progression, and molecules that do not pass quality control are targeted for degradation (144). Properly folded and modified cargo concentrates at ER-exit sites (ERES) and leaves the ER in COPII-coated vesicles (157). These vesicles merge with the ERGIC where cargo destined for the cis-compartment of the GA is sorted from ER resident proteins, which are trafficked back to the ER in COPI-coated vesicles (157). ER exit is often a rate-limiting step in the biosynthesis of transmembrane proteins and is tightly controlled (144). This is true for both AMPA and NMDA receptors of glutamatergic synapses, which exhibit several forms of regulated processing and assembly in the ER (see Chapters by Esteban and Wenthold et al., this volume).

Following exit from the ER, further modifications, including glycosylation and proteolysis, occur as cargo progresses through the cis, medial and trans compartments of the GA (160). Finally, cargo reaches the TGN where it is sorted for either transport to the plasma membrane or endosomal membranes. In most cell types, the ER, ERES and ERGIC elements are dispersed throughout the cell, whereas the Golgi network is located in the pericentriolar area close to the nucleus (160). The anterograde progression of cargo through the secretory pathway therefore involves centrifugal and centripetal displacements of intermediate carriers along microtubule tracks as cargo moves from the ER to the Golgi, and from the TGN to the plasma membrane, respectively (Fig. 1).

2.1.2 Spatial Organization and Unique Features of the Neuronal Secretory Pathway

Although membrane trafficking organelles were observed in neurons over a century ago (81), the fundamental organization of the neuronal secretory pathway is only beginning to emerge. The unique shape and size of neurons dictates a specialized secretory system capable of transporting cargo up to several hundred microns from the cell body to a network of extremely complex dendritic arbors. The neuronal secretory pathway has evolved a unique spatial distribution to allow trafficking of lipids and proteins to the most distal regions of dendrites.

As documented by electron microscopy (EM) studies, the ER extends widely throughout dendrites in addition to the soma (Fig. 2a) (27, 75, 268). Although smooth ER (SER), devoid of ribosomes, dominates in distal dendrites, RER is also found distally (221). Immunogold labeling has shown that the translocon protein Sec61a is present in both the dendritic shaft and in some spines (220, 221). Active ER exit sites also distribute throughout the somato-dendritic compartment as first indicated by direct functional visualization of emerging cargo (105), as well as by the concentration of COPII machinery at discrete puncta in the soma and dendrites (9, 105).

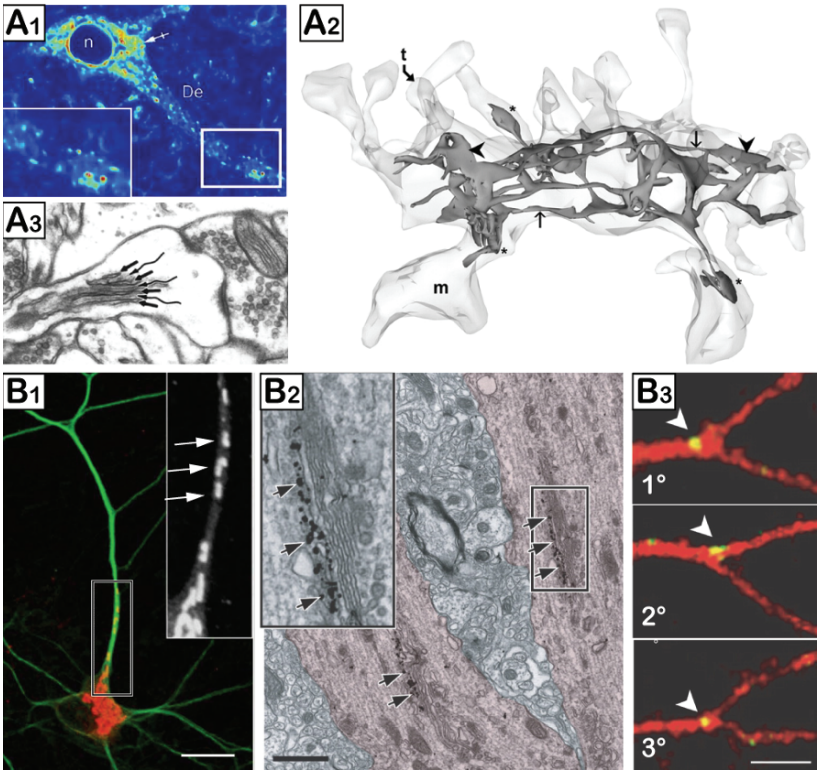

Fig. 2. Dendritic organelles I. Endoplasmic reticulum and Golgi apparatus. (**a**) Endoplasmic Reticulum (ER). (**A1)** Confocal section of a spinal cord neuron immunostained for the ER chaperone protein BiP (*pseudocolored*) illustrating the presence of ER elements throughout dendrites. Adapted from (75); reproduced with permission from the Society for Neuroscience, copyright 2001. (**A2**) Three-dimensional reconstruction of serial electron micrographs showing the distribution of smooth ER (*SER, dark grey*) in dendrites and spines of a CA1 hippocampal neuron. Large flat compartments (*arrowheads*) are linked by thin extensions (*thin arrows*). Note the extension of SER elements in several spines (*asterisks*). Adapted from (47); reprinted with permission from the Society for Neuroscience, copyright 2002. (**A3**) Electron micrograph of the spine apparatus showing the lamination of cisternae (*straight arrows*) between regions of high electron density (*wavy arrows*). Adapted from (268); reproduced with permission from the Society for Neuroscience, copyright 1997. (**b**) Golgi apparatus (GA). (**B1)** Cultured hippocampal neuron stained for MAP2 (*green*), and the cis-Golgi marker GM130 (*red*). Inset: higher magnification of GM130 labeling documenting Golgi outposts dispersed in the apical dendrite (*arrows*). (**B2**) Immunogold labeling for GM130 in adult rat hippocampus demonstrating the presence of mini Golgi-stacks in the apical dendrite of a CA1 pyramidal neuron in vivo. Scale bar, 1 µm. (**B3**) Golgi outposts at dendritic branch points. VSVGts045 (*green*) accumulates at primary, secondary and tertiary dendritic branch points following release from the ER at 20°C. Scale bar, 5 µm. B2–3 adapted from (108); reprinted with permission from Elsevier, copyright 2005.

In addition to its function in lipid biogenesis (21), the SER plays a crucial role in neuronal calcium homeostasis. The SER sequesters calcium by the action of the ER-associated Ca^{2+}-ATPase (SERCA) and releases it in the cytoplasm upon activation of inositol trisphosphate receptors (IP3R) or ryanodine receptors (236, 240). The dendritic SER often extends into the neck of mature spines, providing a conduit to the synapse (Fig. 2a).

In addition to a role as a Ca^{2+} reservoir important for postsynaptic signaling (236), spine SER may also be involved in lipid and protein secretion to the spine surface. A specialized SER-like derivative composed of stacked cisternae, termed the spine apparatus, is found in some dendritic spines (Fig. 2a) (84–86, 268). The presence of vesicles near the tip of the spine apparatus raises the possibility that it could supply membrane for spine growth, and possibly traffic important synaptic proteins, such as AMPA receptors and NMDA receptors, which can be localized to this organelle (200, 227, 268). Though defined largely on morphological criteria, the precise compartmental identity of the spine apparatus has yet to be determined. Notably, the spine apparatus is absent in mice lacking synaptopodin (55). These mice display deficits in LTP and spatial learning, indicating a potential link between the spine apparatus and mechanisms of synaptic plasticity (55).

Spine SER membranes occasionally extend to the periphery of the PSD (288). This tight association of intracellular calcium stores and the PSD may depend on the direct binding of inositol trisphosphate receptors (IP3Rs) in the ER to the postsynaptic scaffold molecule Homer (242). SER membranes are absent from Purkinje neuron spines in *dilute* mice, which lack functional myosin Va (276). Parallel fiber synapses onto Purkine neurons in *dilute* mice have impaired long-term depression, supporting a requirement of spine SER calcium in cerebellar LTD (188).

The organization of the GA in neurons is quite different from what is observed in most non-neuronal cells. Immunofluorescence labeling shows that the neuronal GA consists not only of the perinuclear membrane array found in most cell types, but also of discrete structures dispersed in dendrites, termed Golgi outposts (Fig. 2b) (52, 75, 105, 108, 168, 285). This organization has been confirmed by EM, where miniature Golgi-stacks and intracellular membranes immuno-reactive for Golgi membranes markers such as α-mannosidase II, giantin, GM130, and Rab6, have been observed in dendrites (75, 108, 220). Dendritic Golgi membranes can be found close to synapses but seem to be only localized to the dendritic shaft. Moreover, not all dendrites contain morphological or molecular markers of the GA (108), suggesting dendrite-specific compartmentalization of secretory trafficking.

The dendritic localization of RER, ERES and Golgi membranes suggests that "satellite" secretory systems exist in some dendrites that could locally synthesize and process secretory proteins at sites remote from the cell body. Numerous mRNA species are found in dendrites, including mRNAs encoding postsynaptic receptors such as NMDA receptors, AMPA receptors and glycine receptors (272). Although the local translation of membrane proteins in dendrites is still not as clearly delineated as that of cytoplasmic proteins, protein synthesis and enzymatic activities associated with the secretory pathway, such as glycosylation, persist in hippocampal dendrites isolated from the soma (284, 285). The capacity of isolated dendrites to

synthesize exogenously expressed integral membrane proteins (e.g., glutamate receptors) and deliver them to the plasma membrane has been reported (127, 128).

The involvement of dendritic Golgi ouposts in post-ER membrane trafficking was recently established by imaging hippocampal neurons expressing the ts045 thermosensitive mutant of the vesicular stomatitis viral glycoprotein (VSVG-ts) (105). VSVG-ts is retained in the ER at 39.5°C, but is rapidly released by reducing the temperature to 32°C, allowing control and monitoring of the synchronous progression of cargo through the secretory pathway (16). Upon release from the ER, a fraction of pre-Golgi carriers containing VSVG-ts merge with dendritic compartments immunoreactive for the Golgi markers galactosyltransferase and GM130, demonstrating that dendritic Golgi outposts are functional trafficking platforms (105). Golgi outposts also engage in the local dendritic trafficking of BDNF, confirming their role in processing endogenous proteins (105). The neural cell adhesion molecule (NCAM) promotes the accumulation of TGN-derived vesicles at neuron contact sites (275), indicating that post-Golgi compartments can be directed by intercellular signaling.

Interestingly, at 20°C, a temperature which blocks vesicle budding from the TGN (181), newly released VSVG-ts frequently accumulates at Golgi outposts located at dendritic branch points (Fig. 2b) (105). These outposts engage in ongoing post-Golgi trafficking after release from TGN-exit blockade (105), and appear ideally positioned to regulate the identity or quantity of cargo that is trafficked to each branch, a possibility that awaits further investigation.

Although dendritic Golgi outposts are present in some dendrites of hippocampal and cortical neurons, not all neurons possess detectable dendritic Golgi membranes (105, 108). Moreover, even in those dendrites containing Golgi outposts, the majority of ER-to-Golgi carriers originating in the dendrite are trafficked all the way back to the somatic Golgi in the cell body (105). Thus, dual modes of early secretory trafficking exist in dendrites. The major mode of ER-to-Golgi trafficking is directed long distances to the somatic Golgi apparatus and likely represents the exclusive mode of early secretory trafficking in those dendrites lacking Golgi outposts. A second mode of ER-to-Golgi trafficking occurs locally in dendrites containing Golgi outposts, and may be specialized for the processing of specific cargo or the control of dendritic secretion.

2.2 Dendritic Endosomes

Spines or dendritic segments need to regulate the surface expression of neurotransmitter receptors, adhesion molecules, and ion channels. Often separated by only a few microns, adjacent spines on a dendrite can have strikingly different steady-state levels of synaptic proteins (13, 64, 95, 183), requiring different rates of insertion, removal, and subsequent recycling. The endosomal system provides a primary mechanism for highly localized regulation of spine membrane composition.

The endosomal system is an interconnected and dynamic network of membrane bound structures that receive endocytic vesicles from the plasma membrane (Fig. 1). Newly internalized vesicles formed by means of clathrin-dependent or clathrin-independent endocytosis fuse to form early/sorting endosomes (185). In much the

same way that the TGN functions for secretory proteins, sorting endosomes act as a station from which internalized cargo can be targeted for degradation, transport to the TGN, or recycling back to the cell surface, either directly or via recycling endosomes (Fig. 1) (19). Sorting endosomes display a characteristic tubulo-vesicular morphology directly related to their function. Molecules destined for reinsertion into the plasma membrane or to the TGN exit the sorting endosome on vesicles pinched off from small-diameter tubules (19). Cargo targeted for degradation remains in sorting endosomes which become progressively more acidic as they mature into late endosomes, with degradative cargo budding intraluminally to form multivesicular bodies (MVBs) prior to fusion with lysosomes where cargo degradation is completed within minutes (185). Endocytic organelles exhibit a complex morphological organization in the form of membrane vacuoles, cisternae, tubules, and multilamellar or multivesicular bodies, and differ in their biochemical composition and localization within the cell. In most non-neuronal cells, early endosomes are localized close to the cell periphery while recycling endosomes (REs) are generally found in the peri-centriolar area (Fig. 1) (185). This spatial segregation is likely crucial for the sequential processing of molecules as they progress from one compartment to the other (187). In neurons however, both early and REs are localized in dendrites remote from cell body, potentially facilitating local processing of internalized cargo (63).

The observation of an intracellular accumulation of various plasma proteins in Purkinje neuron dendrites was some of the first evidence for dendritic endocytosis (72). As shown by immunofluorescent labeling of a broad cast of endosome associated proteins, virtually all elements of the endosomal network are present in hippocampal neurons dendrites, including early endosomes, recycling endosomes, late endosomes, and lysosomes (17, 63), although spatial variations in endosome abundance in different dendrites or different neuronal classes has not been thoroughly investigated.

By combining three-dimensional electron microscopy reconstruction of dendrites in vivo with the tracking of internalized gold-conjugated endocytic cargo in acute hippocampal slices, Harris and colleagues have provided important insight into the fundamental organization of the dendritic endosomal network (47). Internal endosomal structures are present in dendrites, including coated and uncoated vesicles, tubular structures and multi-vesicular bodies (Fig. 3a) (47). Interestingly, nearly two thirds of dendritic endosomal structures are situated within or at the base of spines (213), suggesting a direct involvement in subsynaptic membrane trafficking. Endosome-like structures generally extend over stretches of dendrite encompassing one to three spines, suggesting that multiple spines share the same endocytic organelles (47). Clathrin-like coats are present at the tip of some tubular protrusions emerging from these structures, indicating that they may generate smaller trafficking intermediates within the dendritic endosomal pathway (47).

Other studies showed that syntaxin 13, a SNARE protein enriched in early and recycling endosomes, is found in dendritic tubulo-vesicular structures containing transferrin receptors, which are known to be recycled through the endosomal pathway (225). Consistent with local endosomal trafficking, the transferrin receptor continuously cycles back and forth between the dendritic surface and internal structures

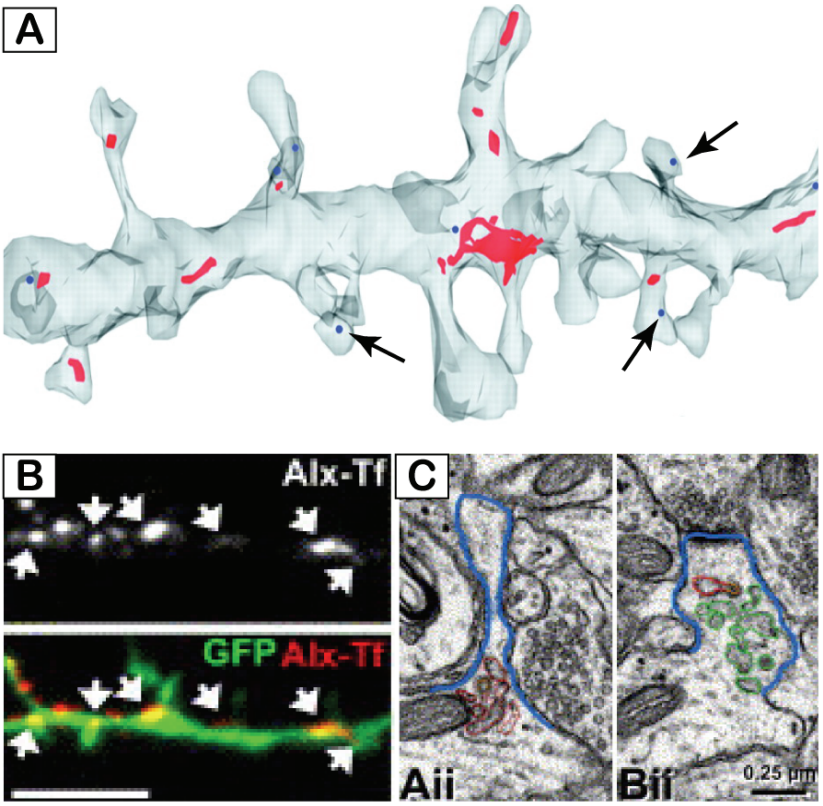

Fig. 3. Dendritic organelles II. Endosomal network. (**a**) Three-dimensional reconstruction of serial electron micrographs showing the distribution of dendritic endosomes in a postnatal day 21 rat hippocampal neuron. Endosomes (*red*) and small vesicles (*blue, arrows*) are distributed throughout dendrites. Adapted from (47); reprinted with permission from the Society for Neuroscience, copyright 2002. (**b**) A cultured hippocampal neuron expressing green fluorescent protein (*GFP, green*) after loading with fluorescent transferrin (*Alx-Tf, red*), showing the presence of recycling endosomes (REs) at the base of dendritic spines (*arrows*). (**c**) Electron micrographs of hippocampal dendritic spines *in vivo* after tracing of the spine surface (*blue lines*), recycling endosomes (*red lines*) and amorphous vesicular clumps (*green lines*). b and c were adapted from (213); reprinted with permission from Elsevier, copyright 2006.

(32, 191, 300). Interestingly, both measurements of transferrin uptake and immunolabeling of hippocampal neuron dendrites indicate that REs are often localized at the base of the spine neck and occasionally in the spine head (Fig. 3b,c) (212, 213). Notably, REs translocate into spines upon LTP-inducing stimuli where they contribute exocytic membrane for spine growth during synapse potentiation (213). These observations demonstrate the presence of a dendritic endosomal network in close proximity to glutamatergic synapses and support a model for local synaptic protein recycling and degradation via endosomes. This issue is discussed in more detail in Sections 3.2. and 3.3.

2.3 Dendritic Mitochondria

Synaptic remodeling requires membrane fission, fusion, protein degradation and local protein synthesis, all of which are ATP-dependent processes. Indeed mitochondria, strongly impregnated by common contrast agents used in electron microscopy, were one of the first dendritic organelles to be identified (217). Dendrite mitochondria are mainly located in the dendritic shaft, but can occasionally be found associated with spines (1, 31). Although dendritic mitochondria usually appear as individual units, three-dimensional EM reconstructions have documented the existence of continuous mitochondrial networks extending over 10–30 μm in dendrites of the CA1 region of rodent hippocampus (222).

Dendritic mitochondria are quite dynamic. In addition to fusion and fission, mitochondria can move over long distances in dendrites in an activity-dependent manner (161). Synaptic stimulation decreases the mobility of mitochondria and induces their translocation into spines (161). Decreased mitochondrial mobility near active synapses and increased mobility in the absence of neural activity would be predicted to distribute mitochondria near highly active, high ATP-utilizing, dendritic regions. Consistent with this notion, reducing the number of dendritic mitochondria by dominant-negative overexpression of the GTPase Drp1, a dynamin-like protein involved in mitochondrial fission, decreased the number of synapses. Conversely, increasing the number of dendritic mitochondria by overexpressing wild type Drp1 or increasing mitochondrial function by treating cells with creatine, nearly doubled synapse number, demonstrating that synapse formation or maintenance is normally limited by mitochondrial activity (161).

3 Polarized Trafficking and Long-Range Targeting to Synapses

The maintenance of synaptic structures with distinct compositions and properties requires continuous and accurate targeting of newly synthesized proteins to their final destination. Like any polarized cell, but amplified due to their morphological complexity, neurons require sorting and targeting mechanisms to ensure the delivery of molecular components to the appropriate compartment. Cell compartmentalization is often most obvious at the plasma membrane where diffusion barriers prevent integral proteins from being freely exchanged from one compartment to another. In neurons, such barriers are present at the axon initial segment, preventing mixing of components of the axonal and somatodendritic membranes (145, 197, 301, 302). On a finer (and possibly more impressive) scale, the thousands of synaptic inputs that a given neuron receives further segment the somatodendritic membrane into an array of postsynaptic microdomains, each with specific compositions. This raises fundamental questions on how such an extreme degree of compartmentalization can be maintained.

3.1 Asymmetric Protein Trafficking in Neurons

Much of what is known about protein trafficking in polarized cells comes from studies in epithelial cells, most prominently the Madin-Darby canine kidney (MDCK) cell-line, which differentiates in vitro into mono-layered epithelia with a well-defined apical/basolateral asymmetry (235). Various modes of polarized trafficking have been described in this system, including selective sorting of cargo into specialized post-Golgi carriers directly targeted to specific cellular domains, and non-specific delivery to the plasma membrane followed by endocytosis and transport to the appropriate destination (235, 289).

Studies in MDCK cells have demonstrated that cargo sorting into distinct post-Golgi carriers relies on intrinsic sequence determinants, with basolateral sorting sequences generally located in the cytoplasmic tail, and apical sorting sequences found frequently in the transmembrane domain (134, 235). Sorting into apical carriers can also result from post-translational modifications, such as N- or O- glycosylation, or addition of a glycosylphosphatidylinositol (GPI) anchor (235). When expressed in neurons, several basolateral and apical proteins are sorted preferentially to the somatodendritic compartment and axon respectively, including VSVG and LDL receptor (basolateral/somatodendritic), and influenza HA protein (apical/axonal) (60, 61, 123). However, more recent experiments suggest that neurons do not recognize some dihydrophobic motifs directing cargo to the basolateral domain in epithelial cells (260). Additionally, the sequence determinant that directs transferrin receptor to the basolateral domain in epithelial cells overlaps only partially with the somatodendritic targeting motif (300). Therefore, while many of the general principles of protein sorting established in epithelial cells apply to neurons, neurons have many of their own rules for establishing protein asymmetry.

In addition to direct delivery of proteins to their final membrane destination, a more circuitous mode of polarized trafficking is observed in certain epithelial and endothelial cells, where cargo destined for the apical plasma membrane is first exocytosed to the basolateral membrane and then endocytosed and transported to the apical membrane (289). Such transcytosis is also observed in neurons and accounts for the trafficking of certain proteins (e.g. VAMP2 and NgCAM/L1), which are initially delivered to the somatodendritic surface but ultimately localize to the presynaptic terminal or axonal membrane (243, 303). Mutations disrupting VAMP2 internalization leave VAMP2 stranded at the somatodendritic surface, indicating that its proper localization requires a redistribution occurring after endocytosis. While NgCAM is enriched in the axonal plasma membrane, intracellular NgCAM containing vesicles are found in both dendrites and axons (30), indicating that the steady state distribution of the molecule does not result from a vectorial targeting of post-Golgi carriers. Monitoring NgCAM insertion in the cell-surface following a synchronous release from the ER revealed that this protein first appears at the somatodendritic plasma membrane, and is subsequently internalized to be trafficked to the axon (243, 303). Interestingly, a single tyrosine point mutation (Y33A) results in direct axonal targeting of NgCAM (303), demonstrating that NgCAM can follow different routes to reach the same final destination. The direct targeting to the axon thus likely represents a default route for some axonal integral proteins.

Another example of polarized trafficking is neuronal potassium channels. Neurons express a wide array of potassium channels, which regulate crucial aspects of cellular ion homeostasis and excitability. Although displaying very similar primary structures within particular subclasses, given channel isoforms can have distinct distribution in the neuronal plasma membrane as well as specific trafficking itineraries (101, 171). For example, while voltage-gated potassium (Kv) channels Kv1.2, Kv1.3 and Kv1.4 are primarily found in the axonal plasma membrane, Kv4.2 is selectively expressed at the somato-dendritic surface (256). The conserved structure and specific surface expression patterns of Kv channels allowed the identification of molecular determinants of asymmetric protein trafficking in neurons. Analysis of chimeric molecules led to the identification of a C-terminal 16 amino acid di-leucine motif required for the proper targeting of Kv4.2 and sufficient to target the axonally localized channels Kv1.3 and Kv1.4 to dendrites (233). Conversely, interaction of the cytoplasmic N-terminal T1 tetramerization domain of Kv1 channels with Kvβ subunits is required for Kv1 expression at the axonal membrane and is sufficient to target dendritic molecules such as the transferrin receptor to the axonal surface (91).

Similar approaches led to the characterization of the molecular address targeting the AMPA receptor GluR1 subunit to the somatodendritic compartment. This determinant resides in the proximal segment of the C-terminal cytoplasmic tail of GluR1 and is sufficient to redirect otherwise axonally expressed proteins such as influenza virus hemagglutinin to the somatodendritic membrane (239).

Finally, of particular interest is the tendency of certain receptors and ion channels to have unusual reverse gradient concentration along dendrites, with distal dendrites displaying a higher concentration of receptors/channels than proximal ones. This is notably the case of AMPA receptors (7, 262) and HCN1 channels (167), whose distance-dependent enrichment along apical dendrites is important for the scaling of dendritic currents and their integration in the soma of hippocampal pyramidal neurons (73). This suggests differential regulation of protein trafficking or stability as a function of dendritic distance, a possibility that still awaits further investigation.

3.2 Polarized Secretory Trafficking for Asymmetric Dendrite Outgrowth

In addition to membrane protein processing, the ER and the Golgi are the primary site of lipid biosynthesis (163), a metabolic function subject to considerable challenge during the massive expansion of the plasma membrane that occurs during neurite outgrowth. Consistent with an immediate requirement for membrane trafficking through the secretory pathway in dendrite growth, disrupting Golgi function with brefeldin A in developing hippocampal or cortical pyramidal neurons dramatically reduces dendritic growth and branching (108). Perhaps more surprisingly, in mature cortical pyramidal neurons the same treatment causes a dramatic simplification of dendrite morphology, demonstrating the importance of an ongoing membrane flux through the secretory pathway for the maintenance of dendritic arbors (108).

The site of membrane insertion in growing dendrites is uncertain, but the spatial organization of the neuronal secretory pathway provides some clues. Somatic Golgi is nearly always oriented toward the apical dendrite in hippocampal pyramidal cells in vivo, and toward the longest and most branched dendrite of hippocampal neurons

in culture (Fig. 2b) (108). As a consequence, most post-Golgi flux originating from the somatic Golgi is directed toward the apical dendrite. Disrupting the polarization of the somatic Golgi by overexpressing GRASP65, a Golgi matrix protein required for cisternal stacking (6), blocks the specification of the apical dendrite without diminishing the overall rate and extent of total dendrite growth (108), demonstrating that polarized post-Golgi trafficking sustains asymmetric dendritic growth.

In another study, the centrosome and associated organelles were found to cluster at sites opposite of the plane of final mitotic division of neural progenitors at a location where the first neurite emerges and becomes the axon (51). However, at slightly later developmental stages after initial neurite outgrowth but before either polarized growth or the appearance of spatially restricted axonal markers (hippocampal neuron polarity stage 1 in the scheme of Banker) (62), the somatic Golgi shows no polarization towards the axon (108). One possibility is that post-Golgi trafficking is redirected from axons to dendrites at different developmental stages, during migration, or in different in vivo contexts. Interestingly, disrupting the secretory pathway by overexpressing a kinase-dead form of protein kinase D1 that prevents cargo budding from the TGN (14), results in cessation of dendritic growth while axonal growth persists over days (108), indicating that distinct mechanisms govern membrane addition to the growing axon. Thus, akin to what occurs during polarization of non-neuronal cell architecture (69, 148), reorganization of the secretory pathway is essential for the asymmetric growth of dendrites. In this context, it is interesting to note that several molecules implicated in neurite polarization and outgrowth, such as PI3K, LIMK1, and Cdk5, are localized to the Golgi apparatus (6, 208, 238), suggesting close coordination between dendritic compartmentalization, polarized cell growth, and directed membrane trafficking through the neuronal Golgi.

3.3 Microtubule Transport

The cytoskeleton provides anchoring points for the stabilization and transport of cellular structures, and is a major determinant of cell architecture. The microtubule network provides tracks along which cargo including organelles, vesicles, and mRNA granules is transported over long distances. In some instances, stabilization of microtubule plus ends allows direct vectorial delivery of cargo to subcompartments of the plasma membrane, as observed for the targeting of gap junction components to epithelial cell adherens junctions (255). In a comparable manner, the establishment of a subsynaptic secretory pathway at the neuromuscular junction (NMJ) or in *Torpedo* electrocytes also involves a local reorganization of microtubules (33, 124–126, 229).

The organization of neuronal microtubules presents interesting specializations. In model non-neuronal cell types, most microtubules share the same polarity and are arranged in a radial manner with their minus end anchored at the microtubule organizing center (MTOC) and their plus end radiating towards the cell periphery (280). In contrast, neuronal microtubules in proximal dendrites adopt both plus end-out and plus end-in orientations while axons and distal dendrites contain microtubules with their plus ends pointing away from the cell body (12). Although the bidirectional

organization of microtubules predicts significant complexity for dendritic membrane trafficking, the precise physiological consequences remain largely unknown.

Active movement of cargo along microtubules requires two classes of motor proteins – the large family of kinesins and cytoplasmic dynein. These microtubule motors move, in most cases, towards the plus and minus ends of microtubules, respectively (293). Indeed, the first kinesin to be described was characterized as the molecular motor responsible for fast axonal transport (23, 294). Subsequently, at least 45 members of the kinesin family have been discovered in mammals (102). Some of these kinesins play distinct roles in dendrites. For example, KIFC2 and KIF5 (the conventional kinesin, also known as kinesin1), localize to the somatodendritic compartment, where they are required for trafficking multivesicular bodies and mRNA granules (137, 241).

In the last ten years, biochemical characterization established that postsynaptic receptors are found with their interacting partners in large protein complexes containing an unexpectedly broad cast of molecular motors, especially kinesins, indicating that receptor microtubule transport is a fundamental aspect of postsynaptic receptor biology (138). This notion has been directly demonstrated for KIF17 which is required for the delivery of NR2B-containing NMDA receptors to synapses (92, 251). Interestingly, interaction with different cargo can "steer" kinesins to specific cellular domains. For example, the glutamate receptor interacting protein 1 (GRIP1), which binds the AMPA receptor subunit GluR2, directs KIF5 primarily to the somatodendritic domain, while a different kinesin binding protein, JSAP1, routes KIF5 to the axon (252). In addition to participating in AMPA receptor trafficking, the GRIP1/KIF5 interaction has important functions in dendrite development and maintenance. Decreasing GRIP1 expression by RNA interference (RNAi) causes a loss of dendrites which can be rescued by overexpression of EphB2 (104), a receptor tyrosine kinase known to affect spine development and synaptic plasticity (117). Conversely, disrupting the GRIP1/KIF5 interaction impairs EphB2 trafficking to dendrites and inhibits dendritic growth, supporting a model where GRIP1 acts as a kinesin adaptor important for dendritic trafficking (104, 252).

In a recent study, Banker and colleagues showed that the behavior of specific kinesins changes during early stages of neuronal morphogenesis. Whereas truncated kinesin 3 accumulates at the tip of all neurites throughout development, truncated kinesin 1 localizes to only a subset of neurites and rapidly redistributes in the emerging axon (119). This event represents one of the earliest molecular readouts of axon specification, and demonstrates that neurite differentiation involves a tight control of the microtubule network and associated kinesin-based transport.

3.4 Synaptic Targeting: Postsynaptic Receptors as Model Cargo

Postsynaptic receptors are highly enriched at synapses, where they form microdomains apposed to presynaptic active zones releasing cognate neurotransmitters. This accumulation depends on postsynaptic scaffolds, which stabilize receptors and connect them to downstream signaling effectors (see Chapter by Kennedy et al., this volume). Time-lapse imaging and photobleaching of GFP-tagged receptors (10, 11, 147, 254, 258) as well as real-time imaging of single fluorescent probes bound to

surface receptors has revealed that receptors continuously diffuse in and out synapses, occasionally exploring multiple synapses (20, 50, 64, 278) (see Chapter by Choquet and Triller, this volume). These latter experimental approaches highlight the highly dynamic and probabilistic nature of receptor stabilization at synapses, emphasizing the importance of lateral diffusion (287). Indeed, upon expressing recombinant glycine receptor subunits under conditions where receptor exocytosis was detected only in the soma, it was found that lateral diffusion is sufficient for receptor accumulation at synapses on distal dendrites (237).

The relative contribution of vesicular trafficking and lateral diffusion to the trafficking of postsynaptic receptors remains a topic of active investigation. In some instances, both modes of trafficking have been found to contribute for a given receptor or membrane cargo. For example, while immunogold labeling and biochemical data suggest that microtubule dependent transport is a major mode of NMDA receptor targeting to synapses, live cell imaging indicates that synapses either receive quantal "packets" of NMDA receptors (299), or can gradually acquire NMDA receptors (25). While the latter study supports a "diffusional" accumulation of NMDA receptors, the former supports a direct delivery by discrete intracellular carriers. Monitoring the recovery of NMDA receptor-mediated synaptic currents following irreversible inactivation with the open-channel blocker MK801 demonstrated that synaptic NMDA receptors exchange with their extrasynaptic counterparts (286). Comparable approaches applied to $GABA_A$ receptors (281) and AMPA receptors (2) support the same general conclusion.

Although lateral diffusion in the plasma membrane is a major aspect of receptor movement and exchange, endocytosis and exocytosis are also crucial for rapid variations of receptor amount at synapses (see Chapters by Esteban, Wenthold et al., Lorena Arancibia-Carcamo et al., and Lisman and Hell, this volume). However, if exo- and endocytosis can occur locally in close proximity to excitatory synapses, membrane fusion and budding have not been demonstrated directly at the PSD (see Section 4 below), implying that lateral diffusion is an obligatory step for receptors to enter or exit synapses (287).

In the case of AMPA receptors, local activity at single synapses reduces the lateral mobility of GluR1, leading to accumulation of receptors by a diffusional trap (64), while local exocytosis from recycling endosomes supplies receptors for LTP (147, 212). Exocytosis and lateral diffusion are thus likely subject to distinct forms of regulation for different classes of receptors and membrane cargo (38, 203). Reconciliation of these two modes of synaptic trafficking (lateral diffusion versus vectorial vesicular targeting) awaits further investigation. Yet, the architecture of the dendritic membrane provides some interesting clues.

Most central excitatory synapses are localized on dendritic spines, and are thus isolated from the dendrite proper by the narrow spine neck, which limits exchange of cytoplasmic and integral membrane proteins between the spine head and the dendritic shaft (10, 11, 18, 232). Local diffusible pools of membrane cargo inside spines would thus provide a reserve pool for synaptic exchange (103). Utilization of vesicular traffic locally within spines, in turn, requires the positioning or mobilization of vesicle budding and trafficking machinery. The combination of a limited local pool of reserve cargo together with spine-localized membrane trafficking

potentially affords exquisite control or "tuning" of molecular abundance at synapses via the balance of exocytosis, endocytosis and diffusional exchange. On the other hand, synapses onto dendritic shafts, including most GABAergic synapses, have direct access to a much larger surface pool of extrasynaptic receptors and are likely less affected by short term changes in the balance between exo- and endocytosis. Such constraints of geometry might help explain the distinct mechanisms for targeting and maintaining postsynaptic membrane components at excitatory spine synapses versus inhibitory shaft synapses (see Chapter by Lorena Arancibia-Carcamo et al., this volume).

3.5 Pre-assembly of Postsynaptic Membranes in the Secretory Pathway

The function of the ER and the Golgi apparatus in membrane trafficking extends beyond transmembrane protein processing. These organelles also direct the trafficking of cytoplasmic proteins modified by acylation. Indeed, acyltransferases, the core enzymes mediating protein palmitoylation localize to the Golgi apparatus (231, 263). The addition of a lipid moiety to proteins increases their hydrophobicity and facilitates their incorporation in lipid rafts (263), which participate in the nano-organization of cellular membranes by stabilizing multi-protein complexes (57, 115). Interestingly, numerous synaptic proteins, including cytoplasmic molecules, are palmitoylated. As shown directly for GRIP, PSD-95, AMPA receptors (GluR1-GluR4), ACh receptors, and $GABA_A$ receptors, palmitoylation regulates synaptic targeting and stabilization (56, 66, 67, 71, 97). PSD-95, the major postsynaptic scaffold protein at glutamateric synapses, is palmitoylated by HIP14, while specific AMPA receptor and $GABA_A$ receptor subunits are palmitoylated by GODZ, two palmitoylating enzymes primarily localized to the Golgi (71, 74, 113, 133, 230, 261).

As described at central synapses (56, 66, 67, 94, 172, 245), and in *Torpedo* electrocytes (175, 176), several postsynaptic scaffold proteins are localized to intracellular membranes containing receptors that likely correspond to compartments of the secretory pathway. Live cell imaging experiments have revealed the appearance and transport of PSD scaffold proteins such as PSD-95 as discrete clusters in dendrites (78, 177, 204). In the case of PSD-95, dendritic transport occurs through the secretory pathway (66) and can be stimulated by BDNF (307). The origin of these "pre-packaged" secretory carriers and the adaptor molecules or coat proteins involved in cargo sorting from earlier stages in the secretory pathway are not yet clear. However, many of these transported scaffold proteins are lipid modified, suggesting that acylation at the Golgi apparatus is an important step in scaffold protein targeting, and may direct the pre-assembly of postsynaptic membranes in the secretory patway. PSD95 is particularly interesting in this regard since its palmitoylation is regulated by synaptic activity (67), and is essential for its co-trafficking with AMPA receptors (66), its targeting to synapses (49, 66), and its ability to cluster transmembrane proteins (41).

4 Local Trafficking of Postsynaptic Components

4.1 Dendritic Exocytosis

4.1.1 Regulated Exocytosis Near the Postsynaptic Membrane

Membrane fusion requires the concerted action of numerous factors to first tether a vesicle to the membrane, prime it for release, and finally to fuse the separate lipid bilayers into a contiguous membrane (120). The eukaryotic membrane fusion machinery has been conserved during evolution, and consists of a core complex of the soluble N-ethylmaleimide sensitive factor attachment protein receptor (SNARE) family of proteins. As elucidated in detail for exocytosis in presynaptic nerve terminals (see Chapter by Atasoy and Kavalali, this volume), vesicle-bound SNARES (v-SNARES) form a complex with target membrane associated SNARES (t-SNARES) through coiled-coil motifs in a process facilitated by members of the Rab family of small GTPases (120). Accessory proteins superimposed on this core machinery allow for regulation of exocytosis by coupling membrane fusion to diverse signaling pathways. Many of the principles governing regulated exocytosis have been established by studies on the Ca^{2+}-dependent release of synaptic vesicles (see Chapter by Atasoy and Kavalali, this volume).

Although less well understood than synaptic vesicle release, dendritic exocytosis has emerged as a key mechanism for regulating synaptic physiology. Among the first indications of regulated exocytosis in dendrites came from experiments demonstrating that the styryl dye FM1-43 accumulates in dendritic TGN-derived compartments and can be rapidly unloaded in response to Ca^2 influx (174). The finding that this activity-dependent dendritic exocytosis required CaMKII (173) pointed towards a direct link between postsynaptic exocytosis and synaptic plasticity signaling pathways. Additional evidence for such a link came from observations that brefeldin A, which disrupts the secretory pathway, impairs synaptic potentiation in hippocampal slices, as does postsynaptic loading of N-ethylmaleimide or botulinum toxin B, two inhibitors of membrane fusion (28, 166). In conjunction with the discovery of silent synapses lacking AMPA receptors (see Chapters by Esteban and Lisman and Hell, this volume), these observations suggested that the rapid insertion of AMPA receptors in the postsynaptic membrane accounted for an early component of the expression of LTP. Subsequent imaging studies demonstrated that AMPA receptors rapidly appear and accumulate near the postsynaptic plasma membrane and are incorporated into synapses in response to stimuli triggering synapse potentiation (45, 147, 212). However, the core machinery for postsynaptic exocytosis and the mechanisms coupling NMDA receptor-induced Ca^{2+} influx to dendritic membrane fusion remain poorly understood. Moreover, the exact location of receptor insertion in the dendritic membrane is unclear, although NMDA receptor-induced exocytic events have recently been visualized in spines (213). For AMPA receptors, either the site of exocytosis or the location of rapid receptor accumulation after exocytosis, depends on subunit composition, since newly inserted GluR2 receptors accumulate more rapidly at synapses than do GluR1 receptors (214, 257). This suggests that a subclass of exocytic vesicles containing distinct populations of receptors may be inserted in close

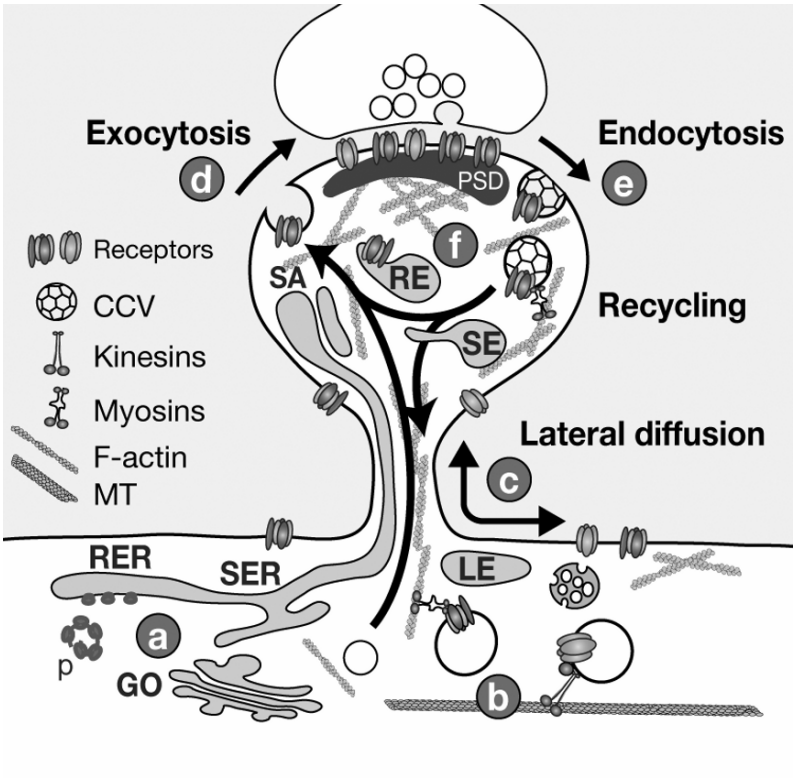

Fig. 4. Model for local trafficking in dendritic spines. Postsynaptic membrane cargo is provided by local synthesis in the secretory pathway (**a**), vesicular transport along microtubules (*dendritic shaft*) and F-actin (*spines*) (**b**), and lateral diffusion in the plasma membrane (**c**). Vesicles are translocated through the spine neck and can release cargo directly in the spine head by exocytosis (**d**). Cargo molecules are stabilized at the postsynaptic membrane but can diffuse in and out the postsynaptic density (PSD). Released receptors and other integral membrane proteins are captured and internalized by the spine endocytic zone located laterally to the PSD (**e**). Internalized receptors are sorted in early/sorting endosomes (SE) and sent either to late endosomes (LE) for degradation, or to recycling endosomes (RE) for return to the spine surface (**f**). *Abbreviations.* SER, smooth endoplasmic reticulum; RER, rough endoplasmic reticulum; GO, Golgi outpost; SA, spine apparatus; PSD, postsynaptic density; CCV, clathrin coated vesicle; SE, sorting endosome; RE, recycling endosome; LE, late endosome; MT, microtubule; p, polysome.

proximity to synapses (Fig. 4). Such exocytic vesicles may derive from recycling endosomes, which traffic into spines and fuse with the spine membrane during LTP-induced potentiation and spine growth (213).

Although initially described at vertebrate NMJs or in *Torpedo* electrocytes (33, 124, 125, 229), sub-synaptic trafficking compartments have been characterized in detail in larval *Drosophila* neuromuscular synapses (179, 180, 266). Genetic approaches in this system have provided important clues to the molecular mechanisms

accounting for postsynaptic exocytosis. For example, the SNARE protein Gtaxin interacts with the postsynaptic scaffolding protein Dlg and is required for the targeted delivery of membranes to the postsynapse (82). In addition, synaptotagmin 4 serves as a Ca^{2+} sensor for postsynaptic exocytosis at the fly neuromuscular synapse (306), suggesting that mechanisms responsible for regulated postsynaptic exocytosis may be very similar to those operating at presynaptic terminals (see Chapter by Atasoy and Kavalali, this volume). Despite these initial clues, many questions remain, such as the identity and requirement for specific molecules that tether postsynaptic vesicles to the plasma membrane, and the nature of machinery linking postsynaptic exocytosis to neural activity.

4.1.2 Rab Proteins and Dendritic Exocytosis

In addition to SNARE proteins, Rab family GTPases are major regulators of membrane trafficking and vesicular fusion. Rab proteins localize to distinct cellular compartments and control trafficking specificity by facilitating interactions between donor and acceptor membranes (90). In general, Rab proteins bind to donor membranes in their GTP-bound state and recruit accessory factors that interact with proteins on the target membrane. When the appropriate combination of vesicle and target membrane proteins is assembled, Rab proteins hydrolyze their bound GTP, locking the vesicle in place for subsequent fusion (90).

Two Rab proteins with well-defined function in non-neuronal cells have been shown to regulate postsynaptic receptor exocytosis. Rab11a controls trafficking through recycling endosomes (291) and is required for NMDA receptor-dependent synapse potentiation including LTP (212). Rab8 is involved in trafficking from the TGN to the cell surface (114) and is also required for the postsynaptic delivery of AMPA receptor subunits (76). Rab11 resides in recycling endosomes, a compartment through which trafficking is mediated by vesicular fusion involving syntaxin 13 (226). Acute disruption of syntaxin 13-dependent trafficking abolishes stimulus-dependent insertion of AMPA receptors and accompanying LTP within minutes (212), suggesting that this membrane trafficking pathway is immediately proximal to NMDA receptor-induced dendritic exocytosis. Still to be determined are the molecular mechanisms underlying synaptic activity-dependent regulation of Rab8 and Rab11. Rab-specific guanine nucleotide exchange factors (GEFs) and GTPase activating proteins (GAPs) orchestrate Rab protein function by controlling their activation and inactivation (79, 250), and are themselves controlled by numerous signaling pathways (250), making them particularly attractive candidates for coupling neural activity to postsynaptic exocytosis.

4.1.3 Myosin Motors and Micron-Range Trafficking of Spine Cargo

In non-neuronal cells, post-TGN transport of secretory cargo to the plasma membrane occurs in two general stages. Vesicles are first transported along microtubules towards the cell-periphery by kinesins, and are then transferred to myosin motors, most prominently class V myosins, which translocate vesicles through the F-actin network of the cell cortex to bring them close to the plasma membrane (152). Myosins

are multisubunit motor molecules that move cargo along F-actin in a unidirectional manner. Myosin motors have diverse functions in vesicle trafficking. At the plasma membrane, myosins control movements of vesicles during exocytosis and endocytosis (152). Many types of myosins are expressed in neurons, and although their individual roles are only beginning to emerge, they seem to be especially important for synaptic receptor recycling (26) (Fig. 4). This is particularly true for class V and class VI myosins, which are enriched in dendritic spines (165, 196, 206). While myosin VI regulates AMPA receptor endocytosis by virtue of its ability to move vesicles inward toward the pointed or minus-ends of actin filaments (206), members of the myosin V family facilitate delivery of AMPA receptors to the dendritic membrane (165).

Interestingly, a light chain common to myosin V and dynein indirectly interacts with AMPA receptors and NMDA receptors via GKAP/PSD95 (196), and class V myosins also associate with specific kinesins (152). Glutamate receptors are thus part of multi-protein complexes containing both microtubule and actin motors, a feature that is likely important for the transfer of receptor containing vesicles from the microtubule-rich dendritic shaft to spines, whose cytoskeleton primarily consists of actin. Recent in vitro experiments demonstrated that myosin Va can traverse filamentous junctions and displays diffusive "scanning" along microtubules (4), emphasizing the ability of this motor to navigate complex cytoskeletal structures.

Class V myosins are calmodulin-binding molecules and are regulated by calcium-dependent conformational changes (279). Increasing calcium triggers a conformational change of myosin Va from a closed, inactive, conformation to an open conformation that exposes the cargo binding domain. Although not yet fully characterized in neurons, this calcium-dependent regulation of class V myosins could play a role in activity-dependent trafficking of cargo to dendritic spines. Indeed myosin Va is highly enriched in the PSD (196, 297). However, *dilute* mutant mice lacking myosin Va have no defects in basal synaptic transmission or LTP at CA1 hippocampal synapses (248) and exhibit no quantitative difference in AMPA receptor abundance at synapses when assessed by immungold electron microscopy (218).

4.1.4 The Exocyst

Genetic studies of targeted membrane trafficking in *S. cerevisiae* led to the identification of conserved proteins important for the late processing of post-Golgi vesicles. Among these proteins were components of the exocyst, an octameric protein complex whose subunits (Sec3, Sec5, Sec6, Sec8, Sec10, Sec15, Exo 70 and Exo84) are required for tethering vesicles to distinct cellular domains (164).

In *Drosophila*, Sec5 and Sec6 mutants display defective neurite outgrowth resulting from impaired exocytosis (192, 193). However, synaptic vesicle exocytosis at the neuromuscular junction is normal in Sec5 mutants, indicating that the exocyst is not involved in all forms of exocytosis (192). Other studies in flies revealed a specific role for Sec15 in axon outgrowth and delivery of a subset of surface proteins to the plasma membrane (e.g. fasciclin II and chaoptin) (186), suggesting that particular components of the exocyst complex play distinct roles in neuronal trafficking.

Components of the exocyst complex are expressed in the mammalian nervous system (112), and notably in the developing brain where Sec6/8 is present in layers displaying ongoing synaptogenesis (98). At later stages, the exocyst is broadly expressed in the adult brain and is enriched in synaptic membranes (112, 244). Consistent with a role in directing exocytosis to discrete domains, Sec6/8 is located at sites of membrane addition, including neurites, filopodia, and growth cones in cultured hippocampal neurons (98, 296). More recently, the exocyst has been shown to participate in the trafficking of glutamate receptors to the synapse. Specifically, Sec8 contains a PDZ-binding motif that interacts with the synaptic scaffolding proteins PSD-95 and SAP102 (244). This interaction thus connects the exocyst complex to NMDA receptors and potentially AMPA receptor/TARP complexes, and is required for NMDA receptor trafficking to the cell surface (244).

The exocyst also plays an important role during late stages of receptor delivery to the plasma membrane, including in the spine head itself. Overexpression of truncated forms of Sec8 and Exo70 uncovered two successive exocyst-dependent steps of AMPA receptor exocytosis required for the turnover of synaptic receptors. Whereas impairment of Sec8 leads to the accumulation of AMPA receptor-containing vesicles in the dendritic shaft, overexpression of Exo70 mutant results in an accumulation of these vesicles in the spine head, leaving them stranded very close to the PSD (77). These data support the notion that AMPA receptor exocytosis can occur directly in spines, and that exocyst subunits play distinct and synergistic functions in the local targeting or tethering of receptor-laden vesicles.

4.2 Dendritic Endocytosis and Post-Endocytic Sorting

Eukaryotic cells continuously invaginate and internalize portions of their plasma membrane to take up extracellular nutrients, trophic factors, and pathogens, as well as to regulate their surface area and control surface levels of membrane proteins. Clathrin-dependent endocytosis is the best characterized mechanism of membrane protein internalization (139), and has been widely studied in presynaptic terminals where it mediates the retrieval of synaptic vesicles (see Chapter by McPherson et al., this volume). Clathrin-mediated endocytosis is initiated by adaptor proteins, such as AP-2, AP-180, and epsin, which associate with phosphoinositides and membrane protein cargo and nucleate the oligomerization of clathrin into a lattice, or coat, apposed to the cytoplasmic face of the plasma membrane (215). Upon acquisition of membrane curvature and invagination, clathrin-coated pits bud from the membrane to form clathrin-coated vesicles (118, 215). The fission reaction is mediated by members of the dynamin family of large GTPases, which assemble into oligomeric rings or spirals around the necks of coated pits (223). All three dynamin family members (dynamins 1–3) are expressed in neurons. While dynamin 2 is ubiquitious and mediates membrane fission in all cells of the body, dynamin 1 is specialized for membrane recycling of synaptic vesicles at the presynaptic terminal following exocytosis (273). Like dynamin 1, dynamin 3 is enriched in brain, but also localizes postsynaptically to dendritic spine heads and may play a role in postsynaptic membrane trafficking (87, 292).

Exocytosis, endocytosis and post-endocytic sorting represent important checkpoints for controlling cell-surface signaling. Although relying on the same basic machinery, turnover rates of surface proteins vary greatly, with internalization time constants ranging from seconds for membrane retrival at presynaptic terminals (273), to minutes in the case of G-protein coupled receptors (GPCRs) (267) and postsynaptic receptors (63, 141, 162). In addition to simply controlling the number of cell-surface receptors, endocytosis is intimately coupled to receptor signaling. A classic example of this is provided by GPCRs and receptor tyrosine kinases (RTKs), whose endocytosis is stimulated by agonist binding, and desensitizes the cell toward the receptor ligand (267). In some cases, endocytosis itself is required for signaling since some receptors initiate signal transduction from internal endosomes (54, 99, 110, 305).

Endocytosis and endosomal sorting of postsynaptic receptors have emerged as key mechanisms for tuning synaptic responses rapidly within minutes, or more slowly during homeostatic scaling and synapse development (45, 290). It is now clear that postsynaptic compartments possess an exquisite degree of specialization for receptor internalization and post-endocytic trafficking (Fig. 4). This specialization is reflected by the diverse stimuli that trigger postsynaptic endocytosis, the complex biochemical interactions that link synaptic receptors to endocytic effectors, and the organization of the spine membrane itself.

4.2.1 Activity-Dependent Regulation of Endocytosis and Post-endocytic Sorting

One indication of an intimate relationship between postsynaptic proteins and endocytic machinery comes from biochemical data showing that postsynaptic receptors and scaffolds directly interact with the endocytic machinery. For example, Homer and mGluR5 interact with dynamin 3 (87), and both the AMPA receptor subunit GluR2 and the NMDA receptor subunit NR2B interact with the AP-2 clathrin adaptor complex (130, 155, 158, 234). The $GABA_A$ receptor subunits β1-3 and γ2 also bind AP-2, indicating that similar mechanisms operate at inhibitory synapses (141). Consistently, interfering with receptor internalization leads to modifications of both excitatory and inhibitory synaptic responses, sometime within minutes (45). Indeed, the regulation of postsynaptic receptor endocytosis is a key set-point for various form of synaptic plasticity.

As initially established for AMPA receptors, internalization rates and post-endocytic sorting are directly modulated by synaptic activity (63, 159, 162). Various mechanisms account for the regulation of AMPA receptor endocytosis, and endocytosis can be triggered either directly by agonist binding, or indirectly by Ca^{2+}- and phosphatase-dependent signaling cascades. Control of postsynaptic receptor internalization involves a broad cast of proteins, including hippocalcin (211), Rab5 (29), CPG2 (48), Arc/Arg3.1. (40), and a significant array of receptor binding partners (45) (see Chapters by Esteban, Wenthold et al., and Lorena Arancibia-Carcamo et al., this volume).

The actin cytoskeleton is a critical determinant of the local dynamics of membrane proteins (150), and actin dynamics are tightly controlled at all steps of endocytosis (68). Accordingly, actin polymerization and depolymerization are required for

stimulus-dependent endocytosis of AMPA receptors (309), and actin plays a critical role in the structural maintenance and plasticity of dendritic spines. It is thus not surprising that spines contain numerous actin regulatory proteins (58). Some of these proteins, notably cortactin (88, 195, 228), Arc/Arg3.1 (40, 170) and myosin VI (206) participate in AMPA receptor endocytosis. In the case of NMDA receptors, the endocytic adaptor PACSIN-1/syndapin-1, which interacts with dynamin and N-WASP and thereby couples actin dynamics to endocytosis (136), directly binds the noncanonical subunit NR3A and drives receptor internalization (216). That actin dynamics is itself regulated by synaptic activity (43, 205, 269) suggests that cytoskeletal remodeling links activity-dependent signaling to the endocytic machinery.

Following endocytosis, the fate of internalized postsynaptic cargo is governed by extrinsic factors such as synaptic activity or metabotropic receptors. For example, while AMPA receptors internalized in response to AMPA stimulation are trafficked to dendritic lysosomes and degraded, receptors internalized in response to NMDA stimulation are sorted into recycling endosomes in a PKA-dependent manner (63). This endosomal sorting is regulated by the duration of the stimulus (265) and can in turn be altered by long-term changes in network activity (159, 201). In a comparable manner, synaptic activity also determines the fate of internalized kainate receptors (178). The subunit composition within a given receptor subtype also modifies the behavior of internalized receptors. In the case of NMDA receptors, NR2A and NR2B subunits contain distinct post-endocytic sorting motifs, which direct them along degradative and recycling pathways, respectively (154). In addition, both NR1 and NR2 subunits contain conserved membrane proximal motifs, which direct internalized receptors for degradation by default if not counteracted by the C-terminal recycling motifs present in NR2B (249).

4.2.2 The Spine Endocytic Zone

By directly visualizing clathrin coats, Blanpied et al. (2002) showed that clathrin puncta localize to most hippocampal dendritic spines in close proximity to the PSD (Fig. 5ab) (17). Live cell imaging together with fluorescence recovery after photobleaching (FRAP) indicated that clathrin repeatedly assembles and disassembles at specific endocytic sites in dendrites and spines (17). The concentration and internalization of labeled transferrin at these spine clathrin puncta established that they are functional, thus demonstrating the existence of stable endocytic zones in close association with the PSD at glutamatergic synapses (17). Ultrastructural analysis confirmed the presence of coated structures in spines in vivo recapitulating all the early stages of the endocytic process (Fig. 5c) (219, 228). Immunogold labeling of its core components revealed an exquisite level of spatial organization of the clathrin endocytic machinery in spines, where AP-2, clathrin and dynamin are localized on the lateral side of the spine surface, with AP-2 closest and dynamin furthest from the PSD (228) (Fig. 5d). In some cases, clathrin and AP-2 are detected at the spine plasma membrane in the absence of a morphologically identified coated pit (228) (Fig. 5d), suggesting a pre-organization of endocytic molecules at the lateral spine membrane.

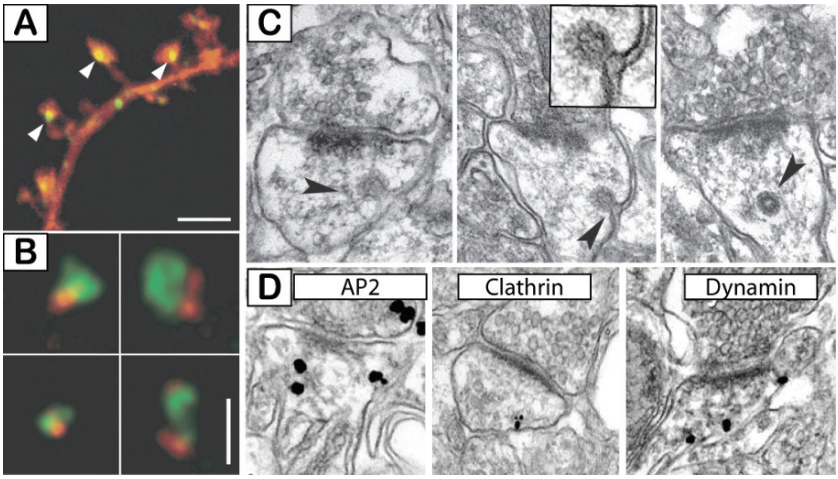

Fig. 5. The spine endocytic zone. (**a**) A cultured hippocampal neuron expressing a cell-fill (*red*) and clathrin-YFP (*green*), illustrating the localization of clathrin puncta to dendritic spine heads (*arrows*). Scale bar, 2 µm. (**b)** Examples of the close association of the spine endocytic zone (*red*) and the PSD (*green*) in hippocampal neurons expressing Clathrin-DsRed and PSD95-GFP. Scale bar, 1 µm. a and b adapted from (17); reprinted with permission from Elsevier, copyright 2002. (**c–d)** Electron micrographs showing the different stages of endocytosis (c) and the distribution of the endocytic machinery (d) in dendritic spine heads of CA1 pyramidal neurons in vivo. c: a clathrin coated invagination prior to scission (*left panel*), a coated invagination (*middle panel*), and a coated vesicle post-scission (*right panel*). d: note the presence of AP-2 (*left panel*), clathrin heavy chain (*middle panel*) and dynamin (*right panel*) immunoreactivity on the lateral side of spines. Adapted from (228); reprinted with permission from Nature Publishing Group, copyright 2004.

These data demonstrate that endocytosis occurs in spines, raising important questions regarding the subsynaptic trafficking via endosomes. Functional studies of the clathrin- and early endosome-associated small GTPase Rab5 showed that it is localized to the perimeter of the PSD and facilitates AMPA receptor internalization in response to LTD-inducing stimuli (29). Rab5 overexpression does not alter the spine/shaft ratio of total (internal and surface) AMPA receptors, but rather selectively decreases the number of receptors at the spine surface (29). This indicates that some internalized receptors remain in the spine, supporting a model where receptors internalized at endocytic zones on the spine surface are retained in a local endosomal pool (Fig. 4).

While the presence of endocytic zones at inhibitory synapses has not been extensively studied, immunolabeling of newly endocytosed $GABA_A$ receptors documented the presence of a stable pool of internalized receptors in close proximity to inhibitory synapses (295). Although the identity of these compartments awaits further investigation, these findings suggest that specialized endocytic machinery may also exist at inhibitory synapses. In this context, it is interesting to note that GRIP1/ABP, a molecule involved in the control of AMPA receptor intracellular trafficking, is also localized to inhibitory synapses and is found in internal membrane compartments containing inhibitory receptors (56, 59, 140), suggesting that the control of inhibitory and excitatory receptor endocytosis might share common effectors in addition to AP-2 and clathrin.

4.2.3 Recycling Endosomes as a Mobilizable Source of Postsynaptic Cargo

Quantitative analysis of AMPA receptor internalization and re-insertion in the plasma membrane in cultured cortical neurons has provided important insight into the involvement of post-endocytic recycling in synaptic remodeling (63, 162). Internalization of cell-surface AMPA receptors occurs with a time constant of approximately 10 min under basal conditions, and reaches a steady state that plateaus after 15–20 min, a time point at which approximately 15–20% of initially labeled receptors are internalized (63, 162). This apparent rate represents a balance between endocytosis itself and cycling of molecules (initially labeled when at the cell-surface) between endosomes and the plasma membrane.

Focusing selectively on the exocytosis of internalized molecules, it was shown that almost 90% of internalized receptors are reinserted in the cell-surface within 60 min under basal conditions, with a similar time constant of 10 min (63). As with internalization, the rate or reinsertion is directly modulated by neuronal activity. This demonstrates that both endocytosis and reinsertion are controlled by activity, and also indicates that the kinetics of reinsertion to the cell-surface can determine the speed and timing of receptor turnover. Adding to this rather complex regulation of trafficking kinetics, selective activation of synaptic AMPA receptors and NMDA receptors can change the compartmental itinerary of internalized cargo by differentially routing internalized AMPA receptors for lysosomal degradation, which in turn leads to changes in the number of receptors in the recycling pool (63, 159, 162). Altogether, these data strongly suggest that recycling endosomes function as a kinetic trap whereby activity-dependent tuning of receptor recycling kinetics and endosomal sorting controls the abundance of postsynaptic receptors in an online fashion (Fig. 4).

As previously mentioned, morphological studies have demonstrated the presence of an endosomal network throughout dendrites, and have specifically shown that recycling endosomes (REs) reside at the base of, and in some instance within, dendritic spines (Fig. 3) (47, 63, 213). This spatial distribution of REs is particularly surprising given that these compartments are usually found in the peri-nuclear area in non-neuronal cells (Fig. 1) (187), and suggests that dendritic REs may play a general role in a local trafficking of postsynaptic cargo. Indeed, whereas some dendritic AMPA receptors are transported to the cell body after endocytosis, an important fraction of internalized receptors remain in dendrites (63, 159, 162). Mechanisms by which different classes of endosomes are positioned in dendrites and spines, and the machinery that determines whether internalized postsynaptic cargo molecules are degraded or locally recycled back to the dendritic surface are only beginning to emerge.

The neuron-enriched endosomal protein of 21 kDa (Neep21) localizes to early endosomes and facilitates recycling of surface receptors (53, 271). In hippocampal neurons Neep21 loss of function decreases recycling of internalized GluR1 and GluR2 (271). This effect is mediated, at least for GluR2, by an activity-dependent interaction between Neep21 and GRIP1, since disrupting this interaction causes GluR2, but not GluR1 or transferrin receptor, to accumulate in early endosomes and lysosomes (270). Consistent with a function of Neep21 in activity-dependent recycling of AMPA receptor, disrupting Neep21 expression in hippocampal slices impairs LTP (3). The activity dependence of the Neep21/GRIP1 interaction suggests

that synaptic activity defines the fraction of internalized receptor that is sorted for recycling at a given synapse, and conversely that this sorting step might tune the amount of receptor available for activity-dependent synaptic potentiation.

Overexpressing dominant-inhibitory mutants of Rab11a, Rme1/EHD1, or syntaxin-13, three molecules required form endocytic recycling, Park et al. (2004) (212) directly tested the role of REs in excitatory receptor trafficking (Fig. 6a). An important finding of this study was that blocking post-endocytic recycling not only decreases the basal level of surface AMPA receptors, but also prevents the rapid NMDA receptor-dependent insertion of GluR1 at hippocampal synapses, as well as LTP expression at Schaffer collateral/CA1 synapses in hippocampal slices. Finally, by selectively tagging or masking those receptors originally at the plasma membrane or those receptors cycling between the cell-surface and endocytic structures, this study established that AMPA receptors rapidly recruited at synapses are mobilized from a pool of internalized molecules, demonstrating the fundamental importance of REs in synapse plasticity.

4.2.4 Endosomal Recycling as a Cellular Basis for Spine Structural Plasticity

While mature neurons maintain their overall size and architecture over years, dendritic spines can be highly dynamic, growing and shrinking over minutes (184, 198). At the scale of the entire cell, endocytosis and exocytosis balance each other to maintain cellular surface area. However, the continuous appearance and disappearance of some dendritic spines necessarily requires increases or decreases in local membrane area. One attractive mechanism for refining spine morphology is local addition or removal of membrane by exocytosis and endocytosis. Indeed, the observation that spine volume correlates with the size of the PSD, the number of postsynaptic AMPA receptors and the abundance of spine endomembranes (100, 169, 182, 283) suggests a quantitative coupling between membrane trafficking, synaptic strength, and spine size. Consistent with this notion, LTP- and LTD-inducing stimuli trigger an increase or decrease in spine size, respectively (151, 183, 194, 207, 308).

The source of membrane for local spine growth has been a matter of debate since the dendritic shaft, and in some cases the spine head itself, house a wide array of endomembranes (135), and remodeling of the actin cytoskeleton alone can expand cellular membranes (70). The recently recognized contribution of endosomal recycling in glutamatergic synapse maintenance and plasticity prompted experiments to test whether REs contribute to spine growth. Combining three-dimensional serial reconstruction electron microscopy and high resolution fluorescence timelapse imaging, Park et al. (2006) (213) showed that spine growth is correlated with both the translocation of endosomal compartments in growing spines and the local exocytosis of RE cargo, occurring in some instances directly in the spine head (Fig. 6b). Furthermore, Rab11a and syntaxin 13 mutants that block endosomal recycling impair stimulus-induced spine growth, thus demonstrating that recycling endosomes contribute membrane material for spine growth (213). By supplying both AMPA receptors (212) and membrane material (213) during LTP, activity-induced cargo transport from recycling endosomes provides an attractive mechanism for coupling functional and structural plasticity at glutamatergic synapses.

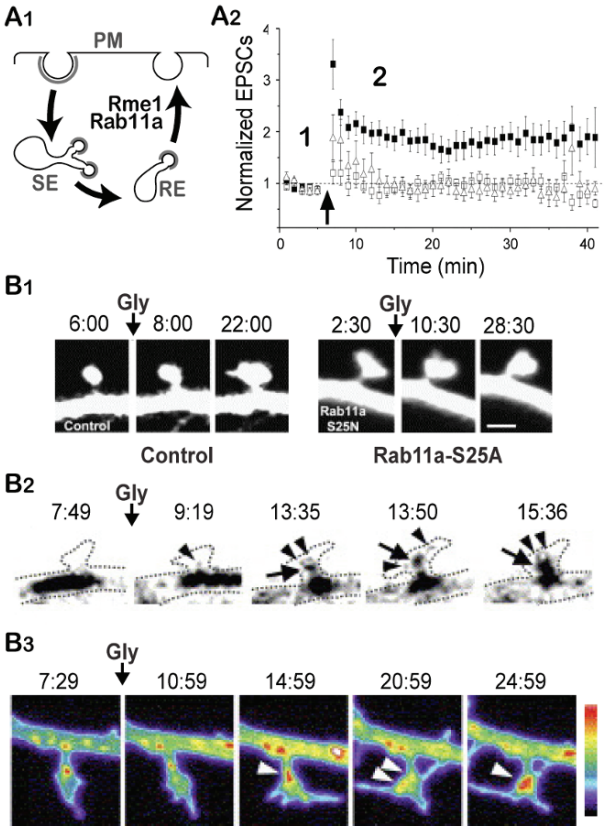

Fig. 6. Recycling endosomes as reservoirs for functional and structural spine plasticity. (**a**) Endosomal recycling is required for the expression of LTP. (**A1**) Schematic diagram showing trafficking pathways between the plasma membrane (PM), sorting endosomes (SE) and recycling endosomes (RE), and the transport step controlled by the regulatory proteins Rab11a and Rme1. (**A2**) Normalized EPSCs at Schaffer collateral/CA1 synapses in hippocampal slices before (1) or after (2) high frequency stimulation (*Arrow*) demonstrating the absence of LTP in cells expressing either Rme1 or Rab11a mutants (open symbols) compared to control cells (black squares). Adapted from (212); reprinted with permission from AAAS, copyright 2004. (**b**) Transport from recycling endosomes is required for activity-induced spine growth. (**B1**) Hippocampal neurons expressing a fluorescent cell fill (tdTomato) before and after a chemical LTP stimulation (Gly). Blocking recycling endosome transport by expression of a Rab11a dominant inhibitory mutant (Rab11a-S25N) prevented stimulus-induced spine growth (*right panel*) as compared to cells expressing GFP (*left panel*). Times indicated in min:sec. (**B2**) Time-lapse sequence of a dendritic spine of a hippocampal neuron expressing a GFP-tagged tranferrin receptor (inverted contrast) before and after a chemical LTP stimulation (Gly) documenting the stimulus-dependent recruitment of recycling endosomes into the spine head. (**B3**) Similar experiment in a neuron expressing a pHluorin-tagged transferrin receptor (TfR) to detect exocytic events in spine (*arrowheads*). B1–3 adapted from (213); reprinted with permission from Elsevier, copyright 2006.

Intriguingly, the importance of Rab11-dependent membrane recycling in the control of cell geometry seems to extend beyond plastic changes of spine morphology, as indicated by the recent characterization of protrudin, a mammalian Rab11-GDP binding protein which promotes and controls neurite formation (259). Spatially directed membrane trafficking from recycling endosomes may thus be a general mechanism for neuronal growth and structural plasticity during the elaboration and remodeling of diverse neural circuits.

5 Concluding Remarks

The discovery that membrane trafficking underlies diverse forms of neuronal plasticity represents a major advance, providing a focal point for experiments addressing the basic mechanisms of learning and memory. Many core issues of neuronal development and circuit plasticity can now be framed as cell biological problems, raising fundamental questions as to how conserved cellular machinery (Fig. 1) has evolved and adapted to serve specialized functions in the mammalian brain. Though far from complete, a picture is emerging of a previously unanticipated and remarkable degree of molecular dynamics at synapses orchestrated by conserved trafficking machinery and diverse dendritic organelles which are regulated by synaptic activity. These molecular dynamics function to maintain reliable, but still exquisitely plastic, communication between highly interconnected cells (Fig. 4). While general rules coupling changes of synaptic strength to membrane trafficking are becoming clarified, our understanding of how cell biological events coordinate neuronal physiology is still constrained by unresolved questions. What controls the organization and distribution of dendritic organelles themselves? To what extent are changes in synaptic strength confined to specific synapses, and under which circumstances? What is the molecular machinery that couples neural activity to dendritic membrane trafficking?

While much recent work has focused on the trafficking of postsynaptic receptors to and from the synapse, it is clear that the trafficking of other synaptic proteins, such as adhesion molecules (83, 224, 247), CaMKII (80), PSD-95 (44, 65, 78, 254), and gephyrin (94, 172) is equally important in tuning synaptic properties (116). A detailed description of the fundamental organization of neuronal organelles will be essential to understand how the regulation of multiprotein complexes produces the requisite integration of diverse signals for coordinating functional and structural plasticity. The relative contribution of long-range versus local trafficking in the development, maintenance, and plasticity of single synapses is not established. Within a given cell, mechanisms accounting for the turnover and plastic changes of synapses vary with synapse localization. For example, recent data suggest that endosomal trafficking and lateral diffusion may differentially contribute to postsynaptic receptors at synapses localized near the soma and those localized to distal dendrites (2). In pyramidal neurons, Golgi outposts are present primarily in apical dendrites (108), suggesting distinct mechanisms in apical versus basolateral dendrites. Indeed synapses onto these dendritic compartments contain different subclasses of NMDA receptors (131), and perhaps other molecules. One possibility is that a heterogeneous spatial restriction of neuronal organelles such as the Golgi apparatus, post-Golgi

compartments, or various classes of endosomes contributes to spatial variation in synapse composition.

At the level of single spines, the actin cytoskeleton is a central effector that couples morphological and functional synaptic plasticity. Although actin can directly affect the organization of the PSD itself (5, 37, 43, 149), its contribution to local spine membrane trafficking is only beginning to emerge. An intriguing observation is that while synaptic activity triggers the recruitment of membrane bound structures in the spine head (213, 282, 283), the diffusional coupling between the spine head and the dendritic shaft is simultaneously decreased (18). A detailed description of spine neck properties will be crucial to understand how calcium signaling, actin dynamics, and membrane trafficking are coordinated to control spine size and molecular composition.

Finally, from a clinical perspective, recent findings illustrate how core issues of dendritic membrane trafficking open new perspectives for therapeutic strategies. For example, the Huntington's disease protein huntingtin binds to proteins such as HIP (huntingtin interacting protein) 1 and HIP14 which participate in the control of inhibitory (142, 143, 156, 209) and excitatory receptor (113) turnover, respectively. The role of postsynaptic trafficking in Alzheimer's disease (AD) is particularly interesting. It has been known for some time that the processing of the amyloid precursor protein during β-amyloid (Aβ) production occurs during trafficking through secretory and endocytic compartments (93), and swollen neuronal endosomes correlate with disease in late-onset AD (34–36, 89, 199). Recent data indicate that Aβ release is activity-dependent, and liberated Aβ in turn attenuates synaptic strength (129) through mechanisms that share similarities with LTD, including increased endocytosis of postsynaptic glutamate receptors (111, 129, 202, 253, 264). Conversely, Aβ oligomers block LTP (298) and presumably AMPA receptor insertion. Thus, it is tempting to speculate that at its early stages, AD is a disorder of postsynaptic trafficking and synapse dysfunction. Beyond neurodegenerative diseases, alterations in glutamate receptor trafficking and defects in synaptic properties have been reported in animal models of neuropsychiatric disorders including addiction (22, 304) and schizophrenia (153), as well as in models of congenital mental retardation (8, 15, 109, 146). Autism has been associated with mutations in specific neuroligin isoforms (121). These mutations impair the expression of these adhesion molecules at the plasma membrane (42, 46), and are likely to have important consequences on synaptic properties given the importance of neuroligins in the clustering of postsynaptic proteins (83, 247). Regulation of dendritic organelles and trafficking machinery is thus requisite for modifying neural circuits during development and plasticity, and provides a novel venue for restoring neuronal function in injury and disease.

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References

1. Adams I and Jones DG. Quantitative ultrastructural changes in rat cortical synapses during early-, mid- and late-adulthood. *Brain Res* 239: 349–363, 1982.
2. Adesnik H, Nicoll RA, and England PM. Photoinactivation of native AMPA receptors reveals their real-time trafficking. *Neuron* 48: 977–985, 2005.
3. Alberi S, Boda B, Steiner P, Nikonenko I, Hirling H, and Muller D. The endosomal protein NEEP21 regulates AMPA receptor-mediated synaptic transmission and plasticity in the hippocampus. *Mol Cell Neurosci* 29: 313–319, 2005.
4. Ali MY, Krementsova EB, Kennedy GG, Mahaffy R, Pollard TD, Trybus KM, and Warshaw DM. Myosin. Va maneuvers through actin intersections and diffuses along microtubules. *Proc Natl Acad Sci USA* 104: 4332–4336, 2007.
5. Allison DW, Chervin AS, Gelfand VI, and Craig AM. Postsynaptic scaffolds of excitatory and inhibitory synapses in hippocampal neurons: maintenance of core components independent of actin filaments and microtubules. *J Neurosci* 20: 4545–4554, 2000.
6. Altan-Bonnet N, Sougrat R, and Lippincott-Schwartz J. Molecular basis for Golgi maintenance and biogenesis. *Curr Opin Cell Biol* 16: 364–372, 2004.
7. Andrasfalvy BK and Magee JC. Distance-dependent increase in AMPA receptor number in the dendrites of adult hippocampal CA1 pyramidal neurons. *J Neurosci* 21: 9151–9159, 2001.
8. Antar LN, Afroz R, Dictenberg JB, Carroll RC, and Bassell GJ. Metabotropic glutamate receptor activation regulates fragile × mental retardation protein and FMR1 mRNA localization differentially in dendrites and at synapses. *J Neurosci* 24: 2648–2655, 2004.
9. Aridor M, Guzik AK, Bielli A, and Fish KN. Endoplasmic reticulum export site formation and function in dendrites. *J Neurosci* 24: 3770–3776, 2004.
10. Ashby MC, De La Rue SA, Ralph GS, Uney J, Collingridge GL, and Henley JM. Removal of AMPA receptors (AMPARs) from synapses is preceded by transient endocytosis of extrasynaptic AMPARs. *J Neurosci* 24: 5172–5176, 2004.
11. Ashby MC, Maier SR, Nishimune A, and Henley JM. Lateral diffusion drives constitutive exchange of AMPA receptors at dendritic spines and is regulated by spine morphology. *J Neurosci* 26: 7046–7055, 2006.
12. Baas PW, Deitch JS, Black MM, and Banker GA. Polarity orientation of microtubules in hippocampal neurons: uniformity in the axon and nonuniformity in the dendrite. *Proc Natl Acad Sci USA* 85: 8335–8339, 1988.
13. Bagal AA, Kao JP, Tang CM, and Thompson SM. Long-term potentiation of exogenous glutamate responses at single dendritic spines. *Proc Natl Acad Sci USA* 102: 14434–14439, 2005.
14. Bard F and Malhotra V. The formation of TGN-to-plasma-membrane transport carriers. *Annu Rev Cell Dev Biol* 22: 439–455, 2006.
15. Bear MF, Huber KM, and Warren ST. The mGluR theory of fragile × mental retardation. *Trends Neurosci* 27: 370–377, 2004.
16. Bergmann JE. Using temperature-sensitive mutants of VSV to study membrane protein biogenesis. *Methods Cell Biol* 32: 85–110, 1989.
17. Blanpied TA, Scott DB, and Ehlers MD. Dynamics and regulation of clathrin coats at specialized endocytic zones of dendrites and spines. *Neuron* 36: 435–449, 2002.
18. Bloodgood BL and Sabatini BL. Neuronal activity regulates diffusion across the neck of dendritic spines. *Science* 310: 866–869, 2005.
19. Bonifacino JS and Rojas R. Retrograde transport from endosomes to the trans-Golgi network. *Nat Rev Mol Cell Biol* 7: 568–579, 2006.
20. Borgdorff AJ and Choquet D. Regulation of AMPA receptor lateral movements. *Nature* 417: 649–653, 2002.

21. Borgese N, Francolini M, and Snapp E. Endoplasmic reticulum architecture: structures in flux. *Curr Opin Cell Biol* 18: 358–364, 2006.
22. Boudreau AC and Wolf ME. Behavioral sensitization to cocaine is associated with increased AMPA receptor surface expression in the nucleus accumbens. *J Neurosci* 25: 9144–9151, 2005.
23. Brady ST. A novel brain ATPase with properties expected for the fast axonal transport motor. *Nature* 317: 73–75, 1985.
24. Bredt DS and Nicoll RA. AMPA receptor trafficking at excitatory synapses. *Neuron* 40: 361–379, 2003.
25. Bresler T, Shapira M, Boeckers T, Dresbach T, Futter M, Garner CC, Rosenblum K, Gundelfinger ED, and Ziv NE. Postsynaptic density assembly is fundamentally different from presynaptic active zone assembly. *J Neurosci* 24: 1507–1520, 2004.
26. Bridgman PC. Myosin-dependent transport in neurons. *J Neurobiol* 58: 164–174, 2004.
27. Broadwell RD and Cataldo AM. The neuronal endoplasmic reticulum: its cytochemistry and contribution to the endomembrane system. I. Cell bodies and dendrites. *J Histochem Cytochem* 31: 1077–1088, 1983.
28. Broutman G and Baudry M. Involvement of the secretory pathway for AMPA receptors in NMDA-induced potentiation in hippocampus. *J Neurosci* 21: 27–34, 2001.
29. Brown TC, Tran IC, Backos DS, and Esteban JA. NMDA receptor-dependent activation of the small GTPase Rab5 drives the removal of synaptic AMPA receptors during hippocampal LTD. *Neuron* 45: 81–94, 2005.
30. Burack MA, Silverman MA, and Banker G. The role of selective transport in neuronal protein sorting. *Neuron* 26: 465–472, 2000.
31. Cameron HA, Kaliszewski CK, and Greer CA. Organization of mitochondria in olfactory bulb granule cell dendritic spines. *Synapse* 8: 107–118, 1991.
32. Cameron PL, Sudhof TC, Jahn R, and De Camilli P. Colocalization of synaptophysin with transferrin receptors: implications for synaptic vesicle biogenesis. *J Cell Biol* 115: 151–164, 1991.
33. Camus G, Jasmin BJ, and Cartaud J. Polarized sorting of nicotinic acetylcholine receptors to the postsynaptic membrane in Torpedo electrocyte. *Eur J Neurosci* 10: 839–852, 1998.
34. Cataldo AM, Barnett JL, Pieroni C, and Nixon RA. Increased neuronal endocytosis and protease delivery to early endosomes in sporadic Alzheimer's disease: neuropathologic evidence for a mechanism of increased beta-amyloidogenesis. *J Neurosci* 17: 6142–6151, 1997.
35. Cataldo AM, Hamilton DJ, Barnett JL, Paskevich PA, and Nixon RA. Properties of the endosomal-lysosomal system in the human central nervous system: disturbances mark most neurons in populations at risk to degenerate in Alzheimer's disease. *J Neurosci* 16: 186–199, 1996.
36. Cataldo AM, Petanceska S, Peterhoff CM, Terio NB, Epstein CJ, Villar A, Carlson EJ, Staufenbiel M, and Nixon RA. App gene dosage modulates endosomal abnormalities of Alzheimer's disease in a segmental trisomy 16 mouse model of down syndrome. *J Neurosci* 23: 6788–6792, 2003.
37. Charrier C, Ehrensperger MV, Dahan M, Levi S, and Triller A. Cytoskeleton regulation of glycine receptor number at synapses and diffusion in the plasma membrane. *J Neurosci* 26: 8502–8511, 2006.
38. Chen L, Chetkovich DM, Petralia RS, Sweeney NT, Kawasaki Y, Wenthold RJ, Bredt DS, and Nicoll RA. Stargazin regulates synaptic targeting of AMPA receptors by two distinct mechanisms. *Nature* 408: 936–943, 2000.
39. Cheng D, Hoogenraad CC, Rush J, Ramm E, Schlager MA, Duong DM, Xu P, Wijayawardana SR, Hanfelt J, Nakagawa T, Sheng M, and Peng J. Relative and absolute quan-

tification of postsynaptic density proteome isolated from rat forebrain and cerebellum. *Mol Cell Proteomics* 5: 1158–1170, 2006.
40. Chowdhury S, Shepherd JD, Okuno H, Lyford G, Petralia RS, Plath N, Kuhl D, Huganir RL, and Worley PF. Arc/Arg3.1 interacts with the endocytic machinery to regulate AMPA receptor trafficking. *Neuron* 52: 445–459, 2006.
41. Christopherson KS, Sweeney NT, Craven SE, Kang R, El-Husseini Ael D, and Bredt DS. Lipid- and protein-mediated multimerization of PSD-95: implications for receptor clustering and assembly of synaptic protein networks. *J Cell Sci* 116: 3213–3219, 2003.
42. Chubykin AA, Liu X, Comoletti D, Tsigelny I, Taylor P, and Sudhof TC. Dissection of synapse induction by neuroligins: effect of a neuroligin mutation associated with autism. *J Biol Chem* 280: 22365–22374, 2005.
43. Colicos MA, Collins BE, Sailor MJ, and Goda Y. Remodeling of synaptic actin induced by photoconductive stimulation. *Cell* 107: 605–616, 2001.
44. Colledge M, Snyder EM, Crozier RA, Soderling JA, Jin Y, Langeberg LK, Lu H, Bear MF, and Scott JD. Ubiquitination regulates PSD-95 degradation and AMPA receptor surface expression. *Neuron* 40: 595–607, 2003.
45. Collingridge GL, Isaac JT, and Wang YT. Receptor trafficking and synaptic plasticity. *Nat Rev Neurosci* 5: 952–962, 2004.
46. Comoletti D, De Jaco A, Jennings LL, Flynn RE, Gaietta G, Tsigelny I, Ellisman MH, and Taylor P. The Arg451Cys-neuroligin-3 mutation associated with autism reveals a defect in protein processing. *J Neurosci* 24: 4889–4893, 2004.
47. Cooney JR, Hurlburt JL, Selig DK, Harris KM, and Fiala JC. Endosomal compartments serve multiple hippocampal dendritic spines from a widespread rather than a local store of recycling membrane. *J Neurosci* 22: 2215–2224, 2002.
48. Cottrell JR, Borok E, Horvath TL, and Nedivi E. CPG2: a brain- and synapse-specific protein that regulates the endocytosis of glutamate receptors. *Neuron* 44: 677–690, 2004.
49. Craven SE, El-Husseini AE, and Bredt DS. Synaptic targeting of the postsynaptic density protein PSD-95 mediated by lipid and protein motifs. *Neuron* 22: 497–509, 1999.
50. Dahan M, Levi S, Luccardini C, Rostaing P, Riveau B, and Triller A. Diffusion dynamics of glycine receptors revealed by single-quantum dot tracking. *Science* 302: 442–445, 2003.
51. de Anda FC, Pollarolo G, Da Silva JS, Camoletto PG, Feiguin F, and Dotti CG. Centrosome localization determines neuronal polarity. *Nature* 436: 704–708, 2005.
52. De Camilli P, Moretti M, Donini SD, Walter U, and Lohmann SM. Heterogeneous distribution of the cAMP receptor protein RII in the nervous system: evidence for its intracellular accumulation on microtubules, microtubule-organizing centers, and in the area of the Golgi complex. *J Cell Biol* 103: 189–203, 1986.
53. Debaigt C, Hirling H, Steiner P, Vincent JP, and Mazella J. Crucial role of neuron-enriched endosomal protein of 21 kDa in sorting between degradation and recycling of internalized G-protein-coupled receptors. *J Biol Chem* 279: 35687–35691, 2004.
54. Delcroix JD, Valletta JS, Wu C, Hunt SJ, Kowal AS, and Mobley WC. NGF signaling in sensory neurons: evidence that early endosomes carry NGF retrograde signals. *Neuron* 39: 69–84, 2003.
55. Deller T, Korte M, Chabanis S, Drakew A, Schwegler H, Stefani GG, Zuniga A, Schwarz K, Bonhoeffer T, Zeller R, Frotscher M, and Mundel P. Synaptopodin-deficient mice lack a spine apparatus and show deficits in synaptic plasticity. *Proc Natl Acad Sci USA* 100: 10494–10499, 2003.
56. DeSouza S, Fu J, States BA, and Ziff EB. Differential palmitoylation directs the AMPA receptor-binding protein ABP to spines or to intracellular clusters. *J Neurosci* 22: 3493–3503, 2002.

57. Di Paolo G and De Camilli P. Phosphoinositides in cell regulation and membrane dynamics. *Nature* 443: 651–657, 2006.
58. Dillon C and Goda Y. The actin cytoskeleton: integrating form and function at the synapse. *Annu Rev Neurosci* 28: 25–55, 2005.
59. Dong H, Zhang P, Liao D, and Huganir RL. Characterization, expression, and distribution of GRIP protein. *Ann NY Acad Sci* 868: 535–540, 1999.
60. Dotti CG, Parton RG, and Simons K. Polarized sorting of glypiated proteins in hippocampal neurons. *Nature* 349: 158–161, 1991.
61. Dotti CG and Simons K. Polarized sorting of viral glycoproteins to the axon and dendrites of hippocampal neurons in culture. *Cell* 62: 63–72, 1990.
62. Dotti CG, Sullivan CA, and Banker GA. The establishment of polarity by hippocampal neurons in culture. *J Neurosci* 8: 1454–1468, 1988.
63. Ehlers MD. Reinsertion or degradation of AMPA receptors determined by activity-dependent endocytic sorting. *Neuron* 28: 511–525, 2000.
64. Ehlers MD, Heine M, Groc L, Lee MC, and Choquet D. Diffusional trapping of GluR1 AMPA receptors by input-specific synaptic activity. *Neuron* 54: 447–460, 2007.
65. Ehrlich I and Malinow R. Postsynaptic density 95 controls AMPA receptor incorporation during long-term potentiation and experience-driven synaptic plasticity. *J Neurosci* 24: 916–927, 2004.
66. El-Husseini AE, Craven SE, Chetkovich DM, Firestein BL, Schnell E, Aoki C, and Bredt DS. Dual palmitoylation of PSD-95 mediates its vesiculotubular sorting, postsynaptic targeting, and ion channel clustering. *J Cell Biol* 148: 159–172, 2000.
67. El-Husseini Ael D, Schnell E, Dakoji S, Sweeney N, Zhou Q, Prange O, Gauthier-Campbell C, Aguilera-Moreno A, Nicoll RA, and Bredt DS. Synaptic strength regulated by palmitate cycling on PSD-95. *Cell* 108: 849–863, 2002.
68. Engqvist-Goldstein AE and Drubin DG. Actin assembly and endocytosis: from yeast to mammals. *Annu Rev Cell Dev Biol* 19: 287–332, 2003.
69. Etienne-Manneville S and Hall A. Integrin-mediated activation of Cdc42 controls cell polarity in migrating astrocytes through PKCzeta. *Cell* 106: 489–498, 2001.
70. Etienne-Manneville S and Hall A. Rho GTPases in cell biology. *Nature* 420: 629–635, 2002.
71. Fang C, Deng L, Keller CA, Fukata M, Fukata Y, Chen G, and Luscher B. GODZ-mediated palmitoylation of GABA(A) receptors is required for normal assembly and function of GABAergic inhibitory synapses. *J Neurosci* 26: 12758–12768, 2006.
72. Fishman PS, Farrand DA, and Kristt DA. Internalization of plasma proteins by cerebellar Purkinje cells. *J Neurol Sci* 100: 43–49, 1990.
73. Frick A, Magee J, Koester HJ, Migliore M, and Johnston D. Normalization of Ca2+ signals by small oblique dendrites of CA1 pyramidal neurons. *J Neurosci* 23: 3243–3250, 2003.
74. Fukata M, Fukata Y, Adesnik H, Nicoll RA, and Bredt DS. Identification of PSD-95 palmitoylating enzymes. *Neuron* 44: 987–996, 2004.
75. Gardiol A, Racca C, and Triller A. Dendritic and postsynaptic protein synthetic machinery. *J Neurosci* 19: 168–179, 1999.
76. Gerges NZ, Backos DS, and Esteban JA. Local control of AMPA receptor trafficking at the postsynaptic terminal by a small GTPase of the Rab family. *J Biol Chem* 279: 43870–43878, 2004.
77. Gerges NZ, Backos DS, Rupasinghe CN, Spaller MR, and Esteban JA. Dual role of the exocyst in AMPA receptor targeting and insertion into the postsynaptic membrane. *EMBO J* 25: 1623–1634, 2006.

78. Gerrow K, Romorini S, Nabi SM, Colicos MA, Sala C, and El-Husseini A. A preformed complex of postsynaptic proteins is involved in excitatory synapse development. *Neuron* 49: 547–562, 2006.
79. Geyer M and Wittinghofer A. GEFs, GAPs, GDIs and effectors: taking a closer (3D) look at the regulation of Ras-related GTP-binding proteins. *Curr Opin Struct Biol* 7: 786–792, 1997.
80. Gleason MR, Higashijima S, Dallman J, Liu K, Mandel G, and Fetcho JR. Translocation of CaM kinase II to synaptic sites in vivo. *Nat Neurosci* 6: 217–218, 2003.
81. Golgi C. On the structure of nerve cells. 1898. *J Microsc* 155: 3–7, 1989.
82. Gorczyca D, Ashley J, Speese S, Gherbesi N, Thomas U, Gundelfinger E, Gramates LS, and Budnik V. Postsynaptic membrane addition depends on the Discs-Large-interacting t-SNARE Gtaxin. *J Neurosci* 27: 1033–1044, 2007.
83. Graf ER, Zhang X, Jin SX, Linhoff MW, and Craig AM. Neurexins induce differentiation of GABA and glutamate postsynaptic specializations via neuroligins. *Cell* 119: 1013–1026, 2004.
84. Gray EG. Axo-somatic and axo-dendritic synapses of the cerebral cortex: an electron microscope study. *J Anat* 93: 420–433, 1959.
85. Gray EG. Electron microscopy of synaptic contacts on dendrite spines of the cerebral cortex. *Nature* 183: 1592–1593, 1959.
86. Gray EG and Guillery RW. A Note on the Dendritic Spine Apparatus. *J Anat* 97: 389–392, 1963.
87. Gray NW, Fourgeaud L, Huang B, Chen J, Cao H, Oswald BJ, Hemar A, and McNiven MA. Dynamin 3 is a component of the postsynapse, where it interacts with mGluR5 and Homer. *Curr Biol* 13: 510–515, 2003.
88. Gray NW, Kruchten AE, Chen J, and McNiven MA. A dynamin-3 spliced variant modulates the actin/cortactin-dependent morphogenesis of dendritic spines. *J Cell Sci* 118: 1279–1290, 2005.
89. Grbovic OM, Mathews PM, Jiang Y, Schmidt SD, Dinakar R, Summers-Terio NB, Ceresa BP, Nixon RA, and Cataldo AM. Rab5-stimulated up-regulation of the endocytic pathway increases intracellular beta-cleaved amyloid precursor protein carboxyl-terminal fragment levels and Abeta production. *J Biol Chem* 278: 31261–31268, 2003.
90. Grosshans BL, Ortiz D, and Novick P. Rabs and their effectors: achieving specificity in membrane traffic. *Proc Natl Acad Sci USA* 103: 11821–11827, 2006.
91. Gu C, Jan YN, and Jan LY. A conserved domain in axonal targeting of Kv1 (Shaker) voltage-gated potassium channels. *Science* 301: 646–649, 2003.
92. Guillaud L, Setou M, and Hirokawa N. KIF17 dynamics and regulation of NR2B trafficking in hippocampal neurons. *J Neurosci* 23: 131–140, 2003.
93. Haass C and Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. *Nat Rev Mol Cell Biol* 8: 101–112, 2007.
94. Hanus C, Vannier C, and Triller A. Intracellular association of glycine receptor with gephyrin increases its plasma membrane accumulation rate. *J Neurosci* 24: 1119–1128, 2004.
95. Harms KJ, Tovar KR, and Craig AM. Synapse-specific regulation of AMPA receptor subunit composition by activity. *J Neurosci* 25: 6379–6388, 2005.
96. Harris KM. Structure, development, and plasticity of dendritic spines. *Curr Opin Neurobiol* 9: 343–348, 1999.
97. Hayashi T, Rumbaugh G, and Huganir RL. Differential regulation of AMPA receptor subunit trafficking by palmitoylation of two distinct sites. *Neuron* 47: 709–723, 2005.
98. Hazuka CD, Foletti DL, Hsu SC, Kee Y, Hopf FW, and Scheller RH. The sec6/8 complex is located at neurite outgrowth and axonal synapse-assembly domains. *J Neurosci* 19: 1324–1334, 1999.

99. Heerssen HM and Segal RA. Location, location, location: a spatial view of neurotrophin signal transduction. *Trends Neurosci* 25: 160–165, 2002.
100. Hering H and Sheng M. Dendritic spines: structure, dynamics and regulation. *Nat Rev Neurosci* 2: 880–888, 2001.
101. Heusser K and Schwappach B. Trafficking of potassium channels. *Curr Opin Neurobiol* 15: 364–369, 2005.
102. Hirokawa N and Takemura R. Molecular motors and mechanisms of directional transport in neurons. *Nat Rev Neurosci* 6: 201–214, 2005.
103. Holcman D and Triller A. Modeling synaptic dynamics driven by receptor lateral diffusion. *Biophys J* 91: 2405–2415, 2006.
104. Hoogenraad CC, Milstein AD, Ethell IM, Henkemeyer M, and Sheng M. GRIP1 controls dendrite morphogenesis by regulating EphB receptor trafficking. *Nat Neurosci* 8: 906–915, 2005.
105. Horton AC and Ehlers MD. Dual modes of endoplasmic reticulum-to-Golgi transport in dendrites revealed by live-cell imaging. *J Neurosci* 23: 6188–6199, 2003.
106. Horton AC and Ehlers MD. Neuronal polarity and trafficking. *Neuron* 40: 277–295, 2003.
107. Horton AC and Ehlers MD. Secretory trafficking in neuronal dendrites. *Nat Cell Biol* 6: 585–591, 2004.
108. Horton AC, Racz B, Monson EE, Lin AL, Weinberg RJ, and Ehlers MD. Polarized secretory trafficking directs cargo for asymmetric dendrite growth and morphogenesis. *Neuron* 48: 757–771, 2005.
109. Hou L, Antion MD, Hu D, Spencer CM, Paylor R, and Klann E. Dynamic translational and proteasomal regulation of fragile × mental retardation protein controls mGluR-dependent long-term depression. *Neuron* 51: 441–454, 2006.
110. Howe CL, Valletta JS, Rusnak AS, and Mobley WC. NGF signaling from clathrin-coated vesicles: evidence that signaling endosomes serve as a platform for the Ras-MAPK pathway. *Neuron* 32: 801–814, 2001.
111. Hsieh H, Boehm J, Sato C, Iwatsubo T, Tomita T, Sisodia S, and Malinow R. AMPAR removal underlies Abeta-induced synaptic depression and dendritic spine loss. *Neuron* 52: 831–843, 2006.
112. Hsu SC, Ting AE, Hazuka CD, Davanger S, Kenny JW, Kee Y, and Scheller RH. The mammalian brain rsec6/8 complex. *Neuron* 17: 1209–1219, 1996.
113. Huang K, Yanai A, Kang R, Arstikaitis P, Singaraja RR, Metzler M, Mullard A, Haigh B, Gauthier-Campbell C, Gutekunst CA, Hayden MR, and El-Husseini A. Huntingtin-interacting protein HIP14 is a palmitoyl transferase involved in palmitoylation and trafficking of multiple neuronal proteins. *Neuron* 44: 977–986, 2004.
114. Huber LA, Pimplikar S, Parton RG, Virta H, Zerial M, and Simons K. Rab8, a small GTPase involved in vesicular traffic between the TGN and the basolateral plasma membrane. *J Cell Biol* 123: 35–45, 1993.
115. Ikonen E. Roles of lipid rafts in membrane transport. *Curr Opin Cell Biol* 13: 470–477, 2001.
116. Inoue A and Okabe S. The dynamic organization of postsynaptic proteins: translocating molecules regulate synaptic function. *Curr Opin Neurobiol* 13: 332–340, 2003.
117. Irie F and Yamaguchi Y. EphB receptors regulate dendritic spine development via intersectin, Cdc42 and N-WASP. *Nat Neurosci* 5: 1117–1118, 2002.
118. Itoh T and De Camilli P. BAR, F-BAR (EFC) and ENTH/ANTH domains in the regulation of membrane-cytosol interfaces and membrane curvature. *Biochim Biophys Acta* 1761: 897–912, 2006.

119. Jacobson C, Schnapp B, and Banker GA. A change in the selective translocation of the Kinesin-1 motor domain marks the initial specification of the axon. *Neuron* 49: 797–804, 2006.
120. Jahn R, Lang T, and Sudhof TC. Membrane fusion. *Cell* 112: 519–533, 2003.
121. Jamain S, Quach H, Betancur C, Rastam M, Colineaux C, Gillberg IC, Soderstrom H, Giros B, Leboyer M, Gillberg C, and Bourgeron T. Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. *Nat Genet* 34: 27–29, 2003.
122. Jan YN and Jan LY. The control of dendrite development. *Neuron* 40: 229–242, 2003.
123. Jareb M and Banker G. The polarized sorting of membrane proteins expressed in cultured hippocampal neurons using viral vectors. *Neuron* 20: 855–867, 1998.
124. Jasmin BJ, Antony C, Changeux JP, and Cartaud J. Nerve-dependent plasticity of the Golgi complex in skeletal muscle fibres: compartmentalization within the subneural sarcoplasm. *Eur J Neurosci* 7: 470–479, 1995.
125. Jasmin BJ, Cartaud J, Bornens M, and Changeux JP. Golgi apparatus in chick skeletal muscle: changes in its distribution during end plate development and after denervation. *Proc Natl Acad Sci USA* 86: 7218–7222, 1989.
126. Jasmin BJ, Changeux JP, and Cartaud J. Compartmentalization of cold-stable and acetylated microtubules in the subsynaptic domain of chick skeletal muscle fibre. *Nature* 344: 673–675, 1990.
127. Ju W, Morishita W, Tsui J, Gaietta G, Deerinck TJ, Adams SR, Garner CC, Tsien RY, Ellisman MH, and Malenka RC. Activity-dependent regulation of dendritic synthesis and trafficking of AMPA receptors. *Nat Neurosci* 7: 244–253, 2004.
128. Kacharmina JE, Job C, Crino P, and Eberwine J. Stimulation of glutamate receptor protein synthesis and membrane insertion within isolated neuronal dendrites. *Proc Natl Acad Sci USA* 97: 11545–11550, 2000.
129. Kamenetz F, Tomita T, Hsieh H, Seabrook G, Borchelt D, Iwatsubo T, Sisodia S, and Malinow R. APP processing and synaptic function. *Neuron* 37: 925–937, 2003.
130. Kastning K, Kukhtina V, Kittler JT, Chen G, Pechstein A, Enders S, Lee SH, Sheng M, Yan Z, and Haucke V. Molecular determinants for the interaction between AMPA receptors and the clathrin adaptor complex AP-2. *Proc Natl Acad Sci USA* 104: 2991–2996, 2007.
131. Kawakami R, Shinohara Y, Kato Y, Sugiyama H, Shigemoto R, and Ito I. Asymmetrical allocation of NMDA receptor epsilon2 subunits in hippocampal circuitry. *Science* 300: 990–994, 2003.
132. Keenan RJ, Freymann DM, Stroud RM, and Walter P. The signal recognition particle. *Annu Rev Biochem* 70: 755–775, 2001.
133. Keller CA, Yuan X, Panzanelli P, Martin ML, Alldred M, Sassoe-Pognetto M, and Luscher B. The gamma2 subunit of GABA (A) receptors is a substrate for palmitoylation by GODZ. *J Neurosci* 24: 5881–5891, 2004.
134. Keller P and Simons K. Post-Golgi biosynthetic trafficking. *J Cell Sci* 110 (Pt 24): 3001–3009, 1997.
135. Kennedy MJ and Ehlers MD. Organelles and trafficking machinery for postsynaptic plasticity. *Annu Rev Neurosci* 29: 325–362, 2006.
136. Kessels MM and Qualmann B. The syndapin protein family: linking membrane trafficking with the cytoskeleton. *J Cell Sci* 117: 3077–3086, 2004.
137. Kiebler MA and Bassell GJ. Neuronal RNA granules: movers and makers. *Neuron* 51: 685–690, 2006.
138. Kim E and Sheng M. PDZ domain proteins of synapses. *Nat Rev Neurosci* 5: 771–781, 2004.
139. Kirchhausen T. Clathrin. *Annu Rev Biochem* 69: 699–727, 2000.

140. Kittler JT, Arancibia-Carcamo IL, and Moss SJ. Association of GRIP1 with a GABA(A) receptor associated protein suggests a role for GRIP1 at inhibitory synapses. *Biochem Pharmacol* 68: 1649–1654, 2004.
141. Kittler JT, Delmas P, Jovanovic JN, Brown DA, Smart TG, and Moss SJ. Constitutive endocytosis of GABAA receptors by an association with the adaptin AP2 complex modulates inhibitory synaptic currents in hippocampal neurons. *J Neurosci* 20: 7972–7977, 2000.
142. Kittler JT and Moss SJ. Modulation of GABAA receptor activity by phosphorylation and receptor trafficking: implications for the efficacy of synaptic inhibition. *Curr Opin Neurobiol* 13: 341–347, 2003.
143. Kittler JT, Thomas P, Tretter V, Bogdanov YD, Haucke V, Smart TG, and Moss SJ. Huntingtin-associated protein 1 regulates inhibitory synaptic transmission by modulating gamma-aminobutyric acid type A receptor membrane trafficking. *Proc Natl Acad Sci USA* 101: 12736–12741, 2004.
144. Kleizen B and Braakman I. Protein folding and quality control in the endoplasmic reticulum. *Curr Opin Cell Biol* 16: 343–349, 2004.
145. Kobayashi T, Storrie B, Simons K, and Dotti CG. A functional barrier to movement of lipids in polarized neurons. *Nature* 359: 647–650, 1992.
146. Koekkoek SK, Yamaguchi K, Milojkovic BA, Dortland BR, Ruigrok TJ, Maex R, De Graaf W, Smit AE, VanderWerf F, Bakker CE, Willemsen R, Ikeda T, Kakizawa S, Onodera K, Nelson DL, Mientjes E, Joosten M, De Schutter E, Oostra BA, Ito M, and De Zeeuw CI. Deletion of FMR1 in Purkinje cells enhances parallel fiber LTD, enlarges spines, and attenuates cerebellar eyelid conditioning in Fragile × syndrome. *Neuron* 47: 339–352, 2005.
147. Kopec CD, Li B, Wei W, Boehm J, and Malinow R. Glutamate receptor exocytosis and spine enlargement during chemically induced long-term potentiation. *J Neurosci* 26: 2000–2009, 2006.
148. Kupfer A, Dennert G, and Singer SJ. Polarization of the Golgi apparatus and the microtubule-organizing center within cloned natural killer cells bound to their targets. *Proc Natl Acad Sci USA* 80: 7224–7228, 1983.
149. Kuriu T, Inoue A, Bito H, Sobue K, and Okabe S. Differential control of postsynaptic density scaffolds via actin-dependent and -independent mechanisms. *J Neurosci* 26: 7693–7706, 2006.
150. Kusumi A, Nakada C, Ritchie K, Murase K, Suzuki K, Murakoshi H, Kasai RS, Kondo J, and Fujiwara T. Paradigm shift of the plasma membrane concept from the two-dimensional continuum fluid to the partitioned fluid: high-speed single-molecule tracking of membrane molecules. *Annu Rev Biophys Biomol Struct* 34: 351–378, 2005.
151. Lang C, Barco A, Zablow L, Kandel ER, Siegelbaum SA, and Zakharenko SS. Transient expansion of synaptically connected dendritic spines upon induction of hippocampal long-term potentiation. *Proc Natl Acad Sci USA* 101: 16665–16670, 2004.
152. Langford GM. Myosin-V, a versatile motor for short-range vesicle transport. *Traffic* 3: 859–865, 2002.
153. Lau CG and Zukin RS. NMDA receptor trafficking in synaptic plasticity and neuropsychiatric disorders. *Nat Rev Neurosci* 8: 413–426, 2007.
154. Lavezzari G, McCallum J, Dewey CM, and Roche KW. Subunit-specific regulation of NMDA receptor endocytosis. *J Neurosci* 24: 6383–6391, 2004.
155. Lavezzari G, McCallum J, Lee R, and Roche KW. Differential binding of the AP-2 adaptor complex and PSD-95 to the C-terminus of the NMDA receptor subunit NR2B regulates surface expression. *Neuropharmacology* 45: 729–737, 2003.

156. Le Clainche C, Pauly BS, Zhang CX, Engqvist-Goldstein AE, Cunningham K, and Drubin DG. A Hip1R-cortactin complex negatively regulates actin assembly associated with endocytosis. *EMBO J*, 26: 1199–1210, 2007.
157. Lee MC, Miller EA, Goldberg J, Orci L, and Schekman R. Bi-directional protein transport between the ER and Golgi. *Annu Rev Cell Dev Biol* 20: 87–123, 2004.
158. Lee SH, Liu L, Wang YT, and Sheng M. Clathrin adaptor AP2 and NSF interact with overlapping sites of GluR2 and play distinct roles in AMPA receptor trafficking and hippocampal LTD. *Neuron* 36: 661–674, 2002.
159. Lee SH, Simonetta A, and Sheng M. Subunit rules governing the sorting of internalized AMPA receptors in hippocampal neurons. *Neuron* 43: 221–236, 2004.
160. Levine CG, Mitra D, Sharma A, Smith CL, and Hegde RS. The efficiency of protein compartmentalization into the secretory pathway. *Mol Biol Cell* 16: 279–291, 2005.
161. Li Z, Okamoto K, Hayashi Y, and Sheng M. The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses. *Cell* 119: 873–887, 2004.
162. Lin JW, Ju W, Foster K, Lee SH, Ahmadian G, Wyszynski M, Wang YT, and Sheng M. Distinct molecular mechanisms and divergent endocytotic pathways of AMPA receptor internalization. *Nat Neurosci* 3: 1282–1290, 2000.
163. Lippincott-Schwartz J, Roberts TH, and Hirschberg K. Secretory protein trafficking and organelle dynamics in living cells. *Annu Rev Cell Dev Biol* 16: 557–589, 2000.
164. Lipschutz JH and Mostov KE. Exocytosis: the many masters of the exocyst. *Curr Biol* 12: R212–214, 2002.
165. Lise MF, Wong TP, Trinh A, Hines RM, Liu L, Kang R, Hines DJ, Lu J, Goldenring JR, Wang YT, and El-Husseini A. Involvement of myosin Vb in glutamate receptor trafficking. *J Biol Chem* 281: 3669–3678, 2006.
166. Lledo PM, Zhang X, Sudhof TC, Malenka RC, and Nicoll RA. Postsynaptic membrane fusion and long-term potentiation. *Science* 279: 399–403, 1998.
167. Lorincz A, Notomi T, Tamas G, Shigemoto R, and Nusser Z. Polarized and compartment-dependent distribution of HCN1 in pyramidal cell dendrites. *Nat Neurosci* 5: 1185–1193, 2002.
168. Lowenstein PR, Morrison EE, Bain D, Shering AF, Banting G, Douglas P, and Castro MG. Polarized distribution of the trans-Golgi network marker TGN38 during the in vitro development of neocortical neurons: effects of nocodazole and brefeldin A. *Eur J Neurosci* 6: 1453–1465, 1994.
169. Luscher C, Nicoll RA, Malenka RC, and Muller D. Synaptic plasticity and dynamic modulation of the postsynaptic membrane. *Nat Neurosci* 3: 545–550, 2000.
170. Lyford GL, Yamagata K, Kaufmann WE, Barnes CA, Sanders LK, Copeland NG, Gilbert DJ, Jenkins NA, Lanahan AA, and Worley PF. Arc, a growth factor and activity-regulated gene, encodes a novel cytoskeleton-associated protein that is enriched in neuronal dendrites. *Neuron* 14: 433–445, 1995.
171. Ma D and Jan LY. ER transport signals and trafficking of potassium channels and receptors. *Curr Opin Neurobiol* 12: 287–292, 2002.
172. Maas C, Tagnaouti N, Loebrich S, Behrend B, Lappe-Siefke C, and Kneussel M. Neuronal cotransport of glycine receptor and the scaffold protein gephyrin. *J Cell Biol* 172: 441–451, 2006.
173. Maletic-Savatic M, Koothan T, and Malinow R. Calcium-evoked dendritic exocytosis in cultured hippocampal neurons. Part II: mediation by calcium/calmodulin-dependent protein kinase II. *J Neurosci* 18: 6814–6821, 1998.
174. Maletic-Savatic M and Malinow R. Calcium-evoked dendritic exocytosis in cultured hippocampal neurons. Part I: trans-Golgi network-derived organelles undergo regulated exocytosis. *J Neurosci* 18: 6803–6813, 1998.

175. Marchand S, Bignami F, Stetzkowski-Marden F, and Cartaud J. The myristoylated protein rapsyn is cotargeted with the nicotinic acetylcholine receptor to the postsynaptic membrane via the exocytic pathway. *J Neurosci* 20: 521–528, 2000.
176. Marchand S, Stetzkowski-Marden F, and Cartaud J. Differential targeting of components of the dystrophin complex to the postsynaptic membrane. *Eur J Neurosci* 13: 221–229, 2001.
177. Marrs GS, Green SH, and Dailey ME. Rapid formation and remodeling of postsynaptic densities in developing dendrites. *Nat Neurosci* 4: 1006–1013, 2001.
178. Martin S and Henley JM. Activity-dependent endocytic sorting of kainate receptors to recycling or degradation pathways. *EMBO J* 23: 4749–4759, 2004.
179. Mathew D, Ataman B, Chen J, Zhang Y, Cumberledge S, and Budnik V. Wingless signaling at synapses is through cleavage and nuclear import of receptor DFrizzled2. *Science* 310: 1344–1347, 2005.
180. Mathew D, Popescu A, and Budnik V. Drosophila amphiphysin functions during synaptic Fasciclin II membrane cycling. *J Neurosci* 23: 10710–10716, 2003.
181. Matlin KS and Simons K. Reduced temperature prevents transfer of a membrane glycoprotein to the cell surface but does not prevent terminal glycosylation. *Cell* 34: 233–243, 1983.
182. Matsuzaki M, Ellis-Davies GC, Nemoto T, Miyashita Y, Iino M, and Kasai H. Dendritic spine geometry is critical for AMPA receptor expression in hippocampal CA1 pyramidal neurons. *Nat Neurosci* 4: 1086–1092, 2001.
183. Matsuzaki M, Honkura N, Ellis-Davies GC, and Kasai H. Structural basis of long-term potentiation in single dendritic spines. *Nature* 429: 761–766, 2004.
184. Matus A. Growth of dendritic spines: a continuing story. *Curr Opin Neurobiol* 15: 67–72, 2005.
185. Maxfield FR and McGraw TE. Endocytic recycling. *Nat Rev Mol Cell Biol* 5: 121–132, 2004.
186. Mehta SQ, Hiesinger PR, Beronja S, Zhai RG, Schulze KL, Verstreken P, Cao Y, Zhou Y, Tepass U, Crair MC, and Bellen HJ. Mutations in Drosophila sec15 reveal a function in neuronal targeting for a subset of exocyst components. *Neuron* 46: 219–232, 2005.
187. Miaczynska M, Pelkmans L, and Zerial M. Not just a sink: endosomes in control of signal transduction. *Curr Opin Cell Biol* 16: 400–406, 2004.
188. Miyata M, Finch EA, Khiroug L, Hashimoto K, Hayasaka S, Oda SI, Inouye M, Takagishi Y, Augustine GJ, and Kano M. Local calcium release in dendritic spines required for long-term synaptic depression. *Neuron* 28: 233–244, 2000.
189. Momiyama A, Silver RA, Hausser M, Notomi T, Wu Y, Shigemoto R, and Cull-Candy SG. The density of AMPA receptors activated by a transmitter quantum at the climbing fibre-Purkinje cell synapse in immature rats. *J Physiol* 549: 75–92, 2003.
190. Moss SJ and Smart TG. Constructing inhibitory synapses. *Nat Rev Neurosci* 2: 240–250, 2001.
191. Mundigl O, Matteoli M, Daniell L, Thomas-Reetz A, Metcalf A, Jahn R, and De Camilli P. Synaptic vesicle proteins and early endosomes in cultured hippocampal neurons: differential effects of Brefeldin A in axon and dendrites. *J Cell Biol* 122: 1207–1221, 1993.
192. Murthy M, Garza D, Scheller RH, and Schwarz TL. Mutations in the exocyst component Sec5 disrupt neuronal membrane traffic, but neurotransmitter release persists. *Neuron* 37: 433–447, 2003.
193. Murthy M, Ranjan R, Denef N, Higashi ME, Schupbach T, and Schwarz TL. Sec6 mutations and the Drosophila exocyst complex. *J Cell Sci* 118: 1139–1150, 2005.
194. Nagerl UV, Eberhorn N, Cambridge SB, and Bonhoeffer T. Bidirectional activity-dependent morphological plasticity in hippocampal neurons. *Neuron* 44: 759–767, 2004.

195. Naisbitt S, Kim E, Tu JC, Xiao B, Sala C, Valtschanoff J, Weinberg RJ, Worley PF, and Sheng M. Shank, a novel family of postsynaptic density proteins that binds to the NMDA receptor/PSD-95/GKAP complex and cortactin. *Neuron* 23: 569–582, 1999.
196. Naisbitt S, Valtschanoff J, Allison DW, Sala C, Kim E, Craig AM, Weinberg RJ, and Sheng M. Interaction of the postsynaptic density-95/guanylate kinase domain- associated protein complex with a light chain of myosin-V and dynein. *J Neurosci* 20: 4524–4534, 2000.
197. Nakada C, Ritchie K, Oba Y, Nakamura M, Hotta Y, Iino R, Kasai RS, Yamaguchi K, Fujiwara T, and Kusumi A. Accumulation of anchored proteins forms membrane diffusion barriers during neuronal polarization. *Nat Cell Biol* 5: 626–632, 2003.
198. Nimchinsky EA, Sabatini BL, and Svoboda K. Structure and function of dendritic spines. *Annu Rev Physiol* 64: 313–353, 2002.
199. Nixon RA. Endosome function and dysfunction in Alzheimer's disease and other neurodegenerative diseases. *Neurobiol Aging* 26: 373–382, 2005.
200. Nusser Z, Lujan R, Laube G, Roberts JD, Molnar E, and Somogyi P. Cell type and pathway dependence of synaptic AMPA receptor number and variability in the hippocampus. *Neuron* 21: 545–559, 1998.
201. O'Brien RJ, Kamboj S, Ehlers MD, Rosen KR, Fischbach GD, and Huganir RL. Activity-dependent modulation of synaptic AMPA receptor accumulation. *Neuron* 21: 1067–1078, 1998.
202. Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kayed R, Metherate R, Mattson MP, Akbari Y, and LaFerla FM. Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. *Neuron* 39: 409–421, 2003.
203. Oh MC, Derkach VA, Guire ES, and Soderling TR. Extrasynaptic membrane trafficking regulated by GluR1 serine 845 phosphorylation primes AMPA receptors for long-term potentiation. *J Biol Chem* 281: 752–758, 2006.
204. Okabe S, Kim HD, Miwa A, Kuriu T, and Okado H. Continual remodeling of postsynaptic density and its regulation by synaptic activity. *Nat Neurosci* 2: 804–811, 1999.
205. Okamoto K, Nagai T, Miyawaki A, and Hayashi Y. Rapid and persistent modulation of actin dynamics regulates postsynaptic reorganization underlying bidirectional plasticity. *Nat Neurosci* 7: 1104–1112, 2004.
206. Osterweil E, Wells DG, and Mooseker MS. A role for myosin VI in postsynaptic structure and glutamate receptor endocytosis. *J Cell Biol* 168: 329–338, 2005.
207. Ostroff LE, Fiala JC, Allwardt B, and Harris KM. Polyribosomes redistribute from dendritic shafts into spines with enlarged synapses during LTP in developing rat hippocampal slices. *Neuron* 35: 535–545, 2002.
208. Paglini G, Peris L, Diez-Guerra J, Quiroga S, and Caceres A. The Cdk5-p35 kinase associates with the Golgi apparatus and regulates membrane traffic. *EMBO Rep* 2: 1139–1144, 2001.
209. Pal A, Severin F, Lommer B, Shevchenko A, and Zerial M. Huntingtin-HAP40 complex is a novel Rab5 effector that regulates early endosome motility and is up-regulated in Huntington's disease. *J Cell Biol* 172: 605–618, 2006.
210. Palade G. Intracellular aspects of the process of protein synthesis. *Science* 189: 347–358, 1975.
211. Palmer CL, Lim W, Hastie PG, Toward M, Korolchuk VI, Burbidge SA, Banting G, Collingridge GL, Isaac JT, and Henley JM. Hippocalcin functions as a calcium sensor in hippocampal LTD. *Neuron* 47: 487–494, 2005.
212. Park M, Penick EC, Edwards JG, Kauer JA, and Ehlers MD. Recycling endosomes supply AMPA receptors for LTP. *Science* 305: 1972–1975, 2004.

213. Park M, Salgado JM, Ostroff L, Helton TD, Robinson CG, Harris KM, and Ehlers MD. Plasticity-induced growth of dendritic spines by exocytic trafficking from recycling endosomes. *Neuron* 52: 817–830, 2006.
214. Passafaro M, Piech V, and Sheng M. Subunit-specific temporal and spatial patterns of AMPA receptor exocytosis in hippocampal neurons. *Nat Neurosci* 4: 917–926, 2001.
215. Pearse BM, Smith CJ, and Owen DJ. Clathrin coat construction in endocytosis. *Curr Opin Struct Biol* 10: 220–228, 2000.
216. Perez-Otano I, Lujan R, Tavalin SJ, Plomann M, Modregger J, Liu XB, Jones EG, Heinemann SF, Lo DC, and Ehlers MD. Endocytosis and synaptic removal of NR3A-containing NMDA receptors by PACSIN1/syndapin1. *Nat Neurosci* 9: 611–621, 2006.
217. Peters A, Palay SL, Webster HF. The fine structure of the nervous system. Oxford: Oxford University Press, 1991.
218. Petralia RS, Wang YX, Sans N, Worley PF, Hammer JA, 3rd, and Wenthold RJ. Glutamate receptor targeting in the postsynaptic spine involves mechanisms that are independent of myosin Va. *Eur J Neurosci* 13: 1722–1732, 2001.
219. Petralia RS, Wang YX, and Wenthold RJ. Internalization at glutamatergic synapses during development. *Eur J Neurosci* 18: 3207–3217, 2003.
220. Pierce JP, Mayer T, and McCarthy JB. Evidence for a satellite secretory pathway in neuronal dendritic spines. *Curr Biol* 11: 351–355, 2001.
221. Pierce JP, van Leyen K, and McCarthy JB. Translocation machinery for synthesis of integral membrane and secretory proteins in dendritic spines. *Nat Neurosci* 3: 311–313, 2000.
222. Popov V, Medvedev NI, Davies HA, and Stewart MG. Mitochondria form a filamentous reticular network in hippocampal dendrites but are present as discrete bodies in axons: a three-dimensional ultrastructural study. *J Comp Neurol* 492: 50–65, 2005.
223. Praefcke GJ and McMahon HT. The dynamin superfamily: universal membrane tubulation and fission molecules? *Nat Rev Mol Cell Biol* 5: 133–147, 2004.
224. Prange O, Wong TP, Gerrow K, Wang YT, and El-Husseini A. A balance between excitatory and inhibitory synapses is controlled by PSD-95 and neuroligin. *Proc Natl Acad Sci USA* 101: 13915–13920, 2004.
225. Prekeris R, Foletti DL, and Scheller RH. Dynamics of tubulovesicular recycling endosomes in hippocampal neurons. *J Neurosci* 19: 10324–10337, 1999.
226. Prekeris R, Klumperman J, Chen YA, and Scheller RH. Syntaxin 13 mediates cycling of plasma membrane proteins via tubulovesicular recycling endosomes. *J Cell Biol* 143: 957–971, 1998.
227. Racca C, Stephenson FA, Streit P, Roberts JD, and Somogyi P. NMDA receptor content of synapses in stratum radiatum of the hippocampal CA1 area. *J Neurosci* 20: 2512–2522, 2000.
228. Racz B, Blanpied TA, Ehlers MD, and Weinberg RJ. Lateral organization of endocytic machinery in dendritic spines. *Nat Neurosci* 7: 917–918, 2004.
229. Ralston E, Lu Z, and Ploug T. The organization of the Golgi complex and microtubules in skeletal muscle is fiber type-dependent. *J Neurosci* 19: 10694–10705, 1999.
230. Rathenberg J, Kittler JT, and Moss SJ. Palmitoylation regulates the clustering and cell surface stability of GABAA receptors. *Mol Cell Neurosci* 26: 251–257, 2004.
231. Resh MD. Fatty acylation of proteins: new insights into membrane targeting of myristoylated and palmitoylated proteins. *Biochim Biophys Acta* 1451: 1–16, 1999.
232. Richards DA, De Paola V, Caroni P, Gahwiler BH, and McKinney RA. AMPA-receptor activation regulates the diffusion of a membrane marker in parallel with dendritic spine motility in the mouse hippocampus. *J Physiol* 558: 503–512, 2004.

233. Rivera JF, Ahmad S, Quick MW, Liman ER, and Arnold DB. An evolutionarily conserved dileucine motif in Shal K+ channels mediates dendritic targeting. *Nat Neurosci* 6: 243–250, 2003.
234. Roche KW, Standley S, McCallum J, Dune Ly C, Ehlers MD, and Wenthold RJ. Molecular determinants of NMDA receptor internalization. *Nat Neurosci* 4: 794–802, 2001.
235. Rodriguez-Boulan E, Kreitzer G, and Musch A. Organization of vesicular trafficking in epithelia. *Nat Rev Mol Cell Biol* 6: 233–247, 2005.
236. Rose CR and Konnerth A. Stores not just for storage. intracellular calcium release and synaptic plasticity. *Neuron* 31: 519–522, 2001.
237. Rosenberg M, Meier J, Triller A, and Vannier C. Dynamics of glycine receptor insertion in the neuronal plasma membrane. *J Neurosci* 21: 5036–5044, 2001.
238. Rosso S, Bollati F, Bisbal M, Peretti D, Sumi T, Nakamura T, Quiroga S, Ferreira A, and Caceres A. LIMK1 regulates Golgi dynamics, traffic of Golgi-derived vesicles, and process extension in primary cultured neurons. *Mol Biol Cell* 15: 3433–3449, 2004.
239. Ruberti F and Dotti CG. Involvement of the proximal C terminus of the AMPA receptor subunit GluR1 in dendritic sorting. *J Neurosci* 20: RC78, 2000.
240. Sabatini BL, Maravall M, and Svoboda K. Ca(2+) signaling in dendritic spines. *Curr Opin Neurobiol* 11: 349–356, 2001.
241. Saito N, Okada Y, Noda Y, Kinoshita Y, Kondo S, and Hirokawa N. KIFC2 is a novel neuron-specific C-terminal type kinesin superfamily motor for dendritic transport of multivesicular body-like organelles. *Neuron* 18: 425–438, 1997.
242. Sala C, Piech V, Wilson NR, Passafaro M, Liu G, and Sheng M. Regulation of dendritic spine morphology and synaptic function by Shank and Homer. *Neuron* 31: 115–130, 2001.
243. Sampo B, Kaech S, Kunz S, and Banker G. Two distinct mechanisms target membrane proteins to the axonal surface. *Neuron* 37: 611–624, 2003.
244. Sans N, Prybylowski K, Petralia RS, Chang K, Wang YX, Racca C, Vicini S, and Wenthold RJ. NMDA receptor trafficking through an interaction between PDZ proteins and the exocyst complex. *Nat Cell Biol* 5: 520–530, 2003.
245. Sans N, Racca C, Petralia RS, Wang YX, McCallum J, and Wenthold RJ. Synapse-associated protein 97 selectively associates with a subset of AMPA receptors early in their biosynthetic pathway. *J Neurosci* 21: 7506–7516, 2001.
246. Schatz G and Dobberstein B. Common principles of protein translocation across membranes. *Science* 271: 1519–1526, 1996.
247. Scheiffele P, Fan J, Choih J, Fetter R, and Serafini T. Neuroligin expressed in nonneuronal cells triggers presynaptic development in contacting axons. *Cell* 101: 657–669, 2000.
248. Schnell E and Nicoll RA. Hippocampal synaptic transmission and plasticity are preserved in myosin Va mutant mice. *J Neurophysiol* 85: 1498–1501, 2001.
249. Scott DB, Michailidis I, Mu Y, Logothetis D, and Ehlers MD. Endocytosis and degradative sorting of NMDA receptors by conserved membrane-proximal signals. *J Neurosci* 24: 7096–7109, 2004.
250. Seabra MC and Wasmeier C. Controlling the location and activation of Rab GTPases. *Curr Opin Cell Biol* 16: 451–457, 2004.
251. Setou M, Nakagawa T, Seog DH, and Hirokawa N. Kinesin superfamily motor protein KIF17 and mLin-10 in NMDA receptor-containing vesicle transport. *Science* 288: 1796–1802, 2000.
252. Setou M, Seog DH, Tanaka Y, Kanai Y, Takei Y, Kawagishi M, and Hirokawa N. Glutamate-receptor-interacting protein GRIP1 directly steers kinesin to dendrites. *Nature* 417: 83–87, 2002.

253. Shankar GM, Bloodgood BL, Townsend M, Walsh DM, Selkoe DJ, and Sabatini BL. Natural oligomers of the Alzheimer amyloid-beta protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. *J Neurosci* 27: 2866–2875, 2007.
254. Sharma K, Fong DK, and Craig AM. Postsynaptic protein mobility in dendritic spines: long-term regulation by synaptic NMDA receptor activation. *Mol Cell Neurosci* 31: 702–712, 2006.
255. Shaw RM, Fay AJ, Puthenveedu MA, von Zastrow M, Jan YN, and Jan LY. Microtubule plus-end-tracking proteins target gap junctions directly from the cell interior to adherens junctions. *Cell* 128: 547–560, 2007.
256. Sheng M, Tsaur ML, Jan YN, and Jan LY. Subcellular segregation of two A-type K+ channel proteins in rat central neurons. *Neuron* 9: 271–284, 1992.
257. Shi S, Hayashi Y, Esteban JA, and Malinow R. Subunit-specific rules governing AMPA receptor trafficking to synapses in hippocampal pyramidal neurons. *Cell* 105: 331–343, 2001.
258. Shi SH, Hayashi Y, Petralia RS, Zaman SH, Wenthold RJ, Svoboda K, and Malinow R. Rapid spine delivery and redistribution of AMPA receptors after synaptic NMDA receptor activation. *Science* 284: 1811–1816, 1999.
259. Shirane M and Nakayama KI. Protrudin induces neurite formation by directional membrane trafficking. *Science* 314: 818–821, 2006.
260. Silverman MA, Peck R, Glover G, He C, Carlin C, and Banker G. Motifs that mediate dendritic targeting in hippocampal neurons: a comparison with basolateral targeting signals. *Mol Cell Neurosci* 29: 173–180, 2005.
261. Singaraja RR, Hadano S, Metzler M, Givan S, Wellington CL, Warby S, Yanai A, Gutekunst CA, Leavitt BR, Yi H, Fichter K, Gan L, McCutcheon K, Chopra V, Michel J, Hersch SM, Ikeda JE, and Hayden MR. HIP14, a novel ankyrin domain-containing protein, links huntingtin to intracellular trafficking and endocytosis. *Hum Mol Genet* 11: 2815–2828, 2002.
262. Smith MA, Ellis-Davies GC, and Magee JC. Mechanism of the distance-dependent scaling of Schaffer collateral synapses in rat CA1 pyramidal neurons. *J Physiol* 548: 245–258, 2003.
263. Smotrys JE and Linder ME. Palmitoylation of intracellular signaling proteins: regulation and function. *Annu Rev Biochem* 73: 559–587, 2004.
264. Snyder EM, Nong Y, Almeida CG, Paul S, Moran T, Choi EY, Nairn AC, Salter MW, Lombroso PJ, Gouras GK, and Greengard P. Regulation of NMDA receptor trafficking by amyloid-beta. *Nat Neurosci* 8: 1051–1058, 2005.
265. Snyder EM, Philpot BD, Huber KM, Dong X, Fallon JR, and Bear MF. Internalization of ionotropic glutamate receptors in response to mGluR activation. *Nat Neurosci* 4: 1079–1085, 2001.
266. Sone M, Suzuki E, Hoshino M, Hou D, Kuromi H, Fukata M, Kuroda S, Kaibuchi K, Nabeshima Y, and Hama C. Synaptic development is controlled in the periactive zones of Drosophila synapses. *Development* 127: 4157–4168, 2000.
267. Sorkin A and Von Zastrow M. Signal transduction and endocytosis: close encounters of many kinds. *Nat Rev Mol Cell Biol* 3: 600–614, 2002.
268. Spacek J and Harris KM. Three-dimensional organization of smooth endoplasmic reticulum in hippocampal CA1 dendrites and dendritic spines of the immature and mature rat. *J Neurosci* 17: 190–203, 1997.
269. Star EN, Kwiatkowski DJ, and Murthy VN. Rapid turnover of actin in dendritic spines and its regulation by activity. *Nat Neurosci* 5: 239–246, 2002.
270. Steiner P, Alberi S, Kulangara K, Yersin A, Sarria JC, Regulier E, Kasas S, Dietler G, Muller D, Catsicas S, and Hirling H. Interactions between NEEP21, GRIP1 and GluR2

regulate sorting and recycling of the glutamate receptor subunit GluR2. *EMBO J* 24: 2873–2884, 2005.
271. Steiner P, Sarria JC, Glauser L, Magnin S, Catsicas S, and Hirling H. Modulation of receptor cycling by neuron-enriched endosomal protein of 21 kD. *J Cell Biol* 157: 1197–1209, 2002.
272. Steward O and Schuman EM. Compartmentalized synthesis and degradation of proteins in neurons. *Neuron* 40: 347–359, 2003.
273. Sudhof TC. The synaptic vesicle cycle. *Annu Rev Neurosci* 27: 509–547, 2004.
274. Sutton MA and Schuman EM. Dendritic protein synthesis, synaptic plasticity, and memory. *Cell* 127: 49–58, 2006.
275. Sytnyk V, Leshchyns'ka I, Delling M, Dityateva G, Dityatev A, and Schachner M. Neural cell adhesion molecule promotes accumulation of TGN organelles at sites of neuron-to-neuron contacts. *J Cell Biol* 159: 649–661, 2002.
276. Takagishi Y, Oda S, Hayasaka S, Dekker-Ohno K, Shikata T, Inouye M, and Yamamura H. The dilute-lethal (dl) gene attacks a Ca2+ store in the dendritic spine of Purkinje cells in mice. *Neurosci Lett* 215: 169–172, 1996.
277. Tanaka J, Matsuzaki M, Tarusawa E, Momiyama A, Molnar E, Kasai H, and Shigemoto R. Number and density of AMPA receptors in single synapses in immature cerebellum. *J Neurosci* 25: 799–807, 2005.
278. Tardin C, Cognet L, Bats C, Lounis B, and Choquet D. Direct imaging of lateral movements of AMPA receptors inside synapses. *EMBO J* 22: 4656–4665, 2003.
279. Taylor KA. Regulation and recycling of myosin V. *Curr Opin Cell Biol* 19: 67–74, 2007.
280. Thery M and Bornens M. Cell shape and cell division. *Curr Opin Cell Biol* 18: 648–657, 2006.
281. Thomas P, Mortensen M, Hosie AM, and Smart TG. Dynamic mobility of functional GABAA receptors at inhibitory synapses. *Nat Neurosci* 8: 889–897, 2005.
282. Toni N, Buchs PA, Nikonenko I, Bron CR, and Muller D. LTP promotes formation of multiple spine synapses between a single axon terminal and a dendrite. *Nature* 402: 421–425, 1999.
283. Toni N, Buchs PA, Nikonenko I, Povilaitite P, Parisi L, and Muller D. Remodeling of synaptic membranes after induction of long-term potentiation. *J Neurosci* 21: 6245–6251, 2001.
284. Torre ER and Steward O. Demonstration of local protein synthesis within dendrites using a new cell culture system that permits the isolation of living axons and dendrites from their cell bodies. *J Neurosci* 12: 762–772, 1992.
285. Torre ER and Steward O. Protein synthesis within dendrites: glycosylation of newly synthesized proteins in dendrites of hippocampal neurons in culture. *J Neurosci* 16: 5967–5978, 1996.
286. Tovar KR and Westbrook GL. Mobile NMDA receptors at hippocampal synapses. *Neuron* 34: 255–264, 2002.
287. Triller A and Choquet D. Surface trafficking of receptors between synaptic and extrasynaptic membranes: and yet they do move! *Trends Neurosci* 28: 133–139, 2005.
288. Tu JC, Xiao B, Naisbitt S, Yuan JP, Petralia RS, Brakeman P, Doan A, Aakalu VK, Lanahan AA, Sheng M, and Worley PF. Coupling of mGluR/Homer and PSD-95 complexes by the Shank family of postsynaptic density proteins. *Neuron* 23: 583–592, 1999.
289. Tuma PL and Hubbard AL. Transcytosis: crossing cellular barriers. *Physiol Rev* 83: 871–932, 2003.
290. Turrigiano GG and Nelson SB. Homeostatic plasticity in the developing nervous system. *Nat Rev Neurosci* 5: 97–107, 2004.
291. Ullrich O, Reinsch S, Urbe S, Zerial M, and Parton RG. Rab11 regulates recycling through the pericentriolar recycling endosome. *J Cell Biol* 135: 913–924, 1996.

292. Urrutia R, Henley JR, Cook T, and McNiven MA. The dynamins: redundant or distinct functions for an expanding family of related GTPases? *Proc Natl Acad Sci USA* 94: 377–384, 1997.
293. Vale RD. The molecular motor toolbox for intracellular transport. *Cell* 112: 467–480, 2003.
294. Vale RD, Reese TS, and Sheetz MP. Identification of a novel force-generating protein, kinesin, involved in microtubule-based motility. *Cell* 42: 39–50, 1985.
295. van Rijnsoever C, Sidler C, and Fritschy JM. Internalized GABA-receptor subunits are transferred to an intracellular pool associated with the postsynaptic density. *Eur J Neurosci* 21: 327–338, 2005.
296. Vega IE and Hsu SC. The exocyst complex associates with microtubules to mediate vesicle targeting and neurite outgrowth. *J Neurosci* 21: 3839–3848, 2001.
297. Walikonis RS, Jensen ON, Mann M, Provance DW, Jr., Mercer JA, and Kennedy MB. Identification of proteins in the postsynaptic density fraction by mass spectrometry. *J Neurosci* 20: 4069–4080, 2000.
298. Walsh DM, Klyubin I, Fadeeva JV, Cullen WK, Anwyl R, Wolfe MS, Rowan MJ, and Selkoe DJ. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. *Nature* 416: 535–539, 2002.
299. Washbourne P, Liu XB, Jones EG, and McAllister AK. Cycling of NMDA receptors during trafficking in neurons before synapse formation. *J Neurosci* 24: 8253–8264, 2004.
300. West AE, Neve RL, and Buckley KM. Identification of a somatodendritic targeting signal in the cytoplasmic domain of the transferrin receptor. *J Neurosci* 17: 6038–6047, 1997.
301. Winckler B, Forscher P, and Mellman I. A diffusion barrier maintains distribution of membrane proteins in polarized neurons. *Nature* 397: 698–701, 1999.
302. Winckler B and Mellman I. Neuronal polarity: controlling the sorting and diffusion of membrane components. *Neuron* 23: 637–640, 1999.
303. Wisco D, Anderson ED, Chang MC, Norden C, Boiko T, Folsch H, and Winckler B. Uncovering multiple axonal targeting pathways in hippocampal neurons. *J Cell Biol* 162: 1317–1328, 2003.
304. Wolf ME, Sun X, Mangiavacchi S, and Chao SZ. Psychomotor stimulants and neuronal plasticity. *Neuropharmacology* 47(Suppl 1): 61–79, 2004.
305. Ye H, Kuruvilla R, Zweifel LS, and Ginty DD. Evidence in support of signaling endosome-based retrograde survival of sympathetic neurons. *Neuron* 39: 57–68, 2003.
306. Yoshihara M, Adolfsen B, Galle KT, and Littleton JT. Retrograde signaling by Syt 4 induces presynaptic release and synapse-specific growth. *Science* 310: 858–863, 2005.
307. Yoshii A and Constantine-Paton M. BDNF induces transport of PSD-95 to dendrites through PI3K-AKT signaling after NMDA receptor activation. *Nat Neurosci* 10: 702–711, 2007.
308. Zhou Q, Homma KJ, and Poo MM. Shrinkage of dendritic spines associated with long-term depression of hippocampal synapses. *Neuron* 44: 749–757, 2004.
309. Zhou Q, Xiao M, and Nicoll RA. Contribution of cytoskeleton to the internalization of AMPA receptors. *Proc Natl Acad Sci USA* 98: 1261–1266, 2001.