SECTION 3

SPECIALIZED AUTOPHAGY: THE NEW FRONTIER

CHAPTER 15

AUTOPHAGY — ROLES IN SYNAPTIC STRUCTURE AND FUNCTION

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ABSTRACT

Macroautophagy is widely studied as a stress-induced response, but the nervous system appears to have adapted this process to modulate synapses under conditions of normal development and plasticity.

INTRODUCTION

Given recent widespread interest in neuronal macroautophagy, it may seem surprising that until recently many biologists believed that this process was absent in neurons[1] and consequently, studies carried out on this topic a decade ago could be substantially delayed in publication. There were nevertheless early reports of neuronal autophagy, including the prescient electron microscopy studies of Leon Roizin in the 1970s that showed high levels of autophagic vacuoles (AVs) in the neurons of patients with Huntington's disease.[2] Studies by Herb Barden indicated that lipofuscin and neuromelanin, the pigments found in neurons of aging brains, were luminal components of autophagic lysosomes,[3] a claim supported in recent years.[4]

As the field was primarily focused on induction of autophagy by amino acid or serum deprivation, it is easy to understand why the existence of neuronal autophagy was often discarded. Neurons are quite resistant under starvation conditions. For example, postnatal neurons can be cultured for weeks in serum-free medium.[5] The lack of readily observed CNS autophagy extended to *in vivo* studies as in food-deprived animals, glycogen, fat, and muscle are rapidly broken down peripherally to supply the brain with nutrients. The hypothalamus, moreover, tightly regulates plasma glucose levels by stimulating release of insulin from the pancreas, which activates mTORC1: this process inhibits autophagy while

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enhancing glucose uptake, decreasing the need for autophagy-derived nutrients.[1,6] It is further possible that turnover of neuronal AVs is rapid, and so observation of AVs is rare under many conditions.[7] Consistent with these observations, AV induction was rarely reported in neuronal cultures or CNS tissue.

We are still at an early stage in understanding the roles of autophagy in the turnover of synaptic components. As of this writing, we are not aware of any studies detailing synaptic functions affected by chaperone-mediated autophagy (CMA), although CMA is involved in the turnover of at least one protein that regulates synaptic function, alpha-synuclein.[8,9] Roles for lysosomal multivesicular bodies at synapses are also relatively unclear. This chapter is thus mostly limited to studies on macroautophagy and associated pathways.

STRESS-INDUCED AUTOPHAGY: IMPLICATIONS FOR NEURONAL MORPHOLOGY

A marked induction of AVs under many forms of neuronal stress is now widely reported.[7,10,11] Neurotoxicity can result from oxidative stress following exposure to L-DOPA, increased cytosolic dopamine (DA), and glutamate-triggered excitoxocity, each of which induce autophagy.[12–14] Neurodegenerative disorders such as Parkinson's disease (PD),[15] Huntington's disease,[16–18] prion diseases,[19,20] and Alzheimer's disease[21] are also associated with increased autophagy. (***see also Section 2 and Chapter 5***). For example, leucine-rich repeat kinase 2 (LRRK2) mutations implicated in Parkinson's disease appear to decrease neurite outgrowth via effects on AVs, in part via effects on LC3 phosphorylation (see below).[22,23]

In some instances of neurodegeneration and neurotoxicity, stress-induced autophagy is related to altered/compromised neurites and synapses. For example, the presence of AVs at presynaptic terminals and dendritic spines has been documented in patients with transmissible spongiform encephalopathies, implicating macroautophagy in the loss of synapses,[19,20] and the authors speculate that entire synapses damaged by disease could be degraded via autophagy. AVs accumulate in early stages of neurodegeneration in some models, and inhibition of their formation can suppress degeneration.[24]

Classic axonal *Wallerian* or anterograde degeneration, in which the axon distal to scission from the cell body degenerates, may involve autophagy:[25] it is indeed difficult to fathom how else large amounts of neuritic material are selectively degraded in the absence of an alternate means to mark neurites for phagocytosis. Recent work on the nigrostriatal dopaminergic projection indicates a role for macroautophagy in retrograde axonal degeneration as well, in that a protective

effect of Akt following axotomy may be due to enhanced mTOR activity, which suppresses AV formation.[26]

A striking example of neurite alteration associated with stress-induced autophagy occurs with methamphetamine, a drug long known to produce neurotoxic loss of dopaminergic axons. Axonal loss appears to be caused by a redistribution of DA from synaptic vesicles in the terminals to the cytoplasm,[27,28] where it produces reactive oxygen species that trigger macroautophagy as a stress-induced response. This induction of autophagy in cultured neurons by methamphetamine is associated with a nearly complete loss of neurites in the absence of cell body loss.[13] The collapse of lysosomal pH gradients by the "weak base" effects of methamphetamine[29] disrupts the function of lysosomal proteases and further contributes to a buildup of AVs, so that cultured DA neurons without neurites exhibit massive levels of AVs in the cell body.

In the case of excitotoxicity, Purkinje cells and hippocampal neurons of Lurcher mice, which express constitutively active delta2 glutamate receptors (GluRδ2), exhibit dystrophic axons with focal swellings that contain AVs. Autophagy is induced due to an increase in Na^+ influx, which also leads to neuronal depolarization and increased $Ca2^+$ influx through voltage-gated calcium channels. Increased cytosolic $Ca2^+$ ultimately results in cell death via activation of calpains.[30–32] As genetic deletion of Atg5, an essential macroautophagy-related gene, exacerbates cell death, macroautophagy appears to provide a protective function,[31] although this issue is not yet clear, in part due to the age at which the protein becomes deficient.[33] The balance between excitatory stress and ongoing autophagy as a stress-induced response could be particularly important for maintaining normal neuronal function under conditions of high cytosolic $Ca2^+$.

Accumulation of AVs in axons may also be predicted in lysosomal storage disorders as both a stress induced response and decreased AV turnover.[4] Indeed, axonal AV accumulation is reported in mouse models of Batten disease expressing mutant lysosomal cathepsin enzymes[34] and is implicated in dysfunction of hippocampal GABAergic interneurons in cathepsin D-deficient mice.[35]

ROLES FOR MACROAUTOPHAGY IN NEURITE REMODELING AND RETRACTION

In contrast to its role as a response to neurodegenerative or toxic stress, what role does autophagy play under normal conditions in the normal turnover of synaptic components and/or neurites? mTOR signaling, which regulates protein synthesis and autophagy induction, is implicated in synaptic plasticity, including the maintenance of hippocampal long term potentiation.[36] Synapse disassembly or

"pruning" has also been implicated in normal development and during learning and memory.[37] Thus, alterations in synaptic structure involving clearance of synaptic components, including secretory vesicles, receptors and transporters, and mitochondria, with attendant changes in synaptic function, might rely on autophagy.[38]

Early evidence that neuronal autophagy sculpts neurites was provided in Mary Bartlett Bunge's 1973 study on the presence of AVs in retracting neuronal processes of rat sympathetic motor neurons, indicating that neuronal remodeling could occur through autophagic clearance.[39] She described the local formation of lysosomal-like structures at the growth cone and the presence of AVs at various stages of formation along nerve fibers.

Peter Hollenbeck (1993) expanded on these findings by demonstrating that AVs formed in the distal regions of axons in cultured sympathetic neurons.[40] AVs accumulated both cytosolic and endocytic products. Following trituration, localization of Texas red-dextran label in the cytosol changed from diffuse to punctuate within 72 hours, indicating sequestration by AVs. At the axonal growth cone, Lucifer yellow in the medium was sequestered by neurons into AVs, which then travelled along the axon back to the cell body, corroborating the notion that endocytic structures and their contents can be degraded through amphisomes/AVs in neurons.

Hollenbeck reported both retrograde and anterograde movement of AVs. The net direction of movement of these organelles was tightly coupled to the energetic state of the neuron. Hollenbeck demonstrated this concept using forskolin, which enhances cAMP levels and has more recently been found to promote phosphorylation of LC3, which inhibits autophagy,[23] and the actin polymerization inhibitor, cytochalasin. Forskolin caused AVs to move anterogradely, thus supplying the growth cone with nutrients and membrane, while cytocholasin favored retrograde transport and inhibited axonal growth. These findings suggest that neurons modulate autophagy in a dynamic manner to fit their physiological requirements, and Hollenbeck's study introduced the idea that the rate and vector of AV movement allows neurons to redistribute membrane and alter neuronal structure.

More recent studies have identified roles for Ulk1/Atg1, a protein kinase involved in AV formation and axonal transport, in neurite remodeling. (The term Ulk1 is most commonly used for a mammalian Atg1 homologue.) In Drosophila, disruption of AV formation or AV-lysosomal fusion decreased the size of the neuromuscular junction (NMJ), while overexpression of Atg1 enhanced autophagy and increased the number of synaptic boutons and neuritic branches. Consistently, exposure of wild type *Drosophila* to the mTOR inhibitor, rapamycin,[7] resulted in synaptic overgrowth.[41] Deletion of *unc-51*, a homologue of *atg1*, in Drosophila

resulted in glutamate receptor clusters unapposed to Bruchpilot, an active zone protein, the development of aberrant synapses with fewer active zones, a decrease in the density of synapses in general, and a decrease in evoked neurotransmitter release at the Drosophila NMJ.[42] In another *Drosophila* model, deletion of *unc-51* resulted in accumulation of synaptic vesicles in axon shafts, a decrease in the number of synaptic boutons, and the clustering of dense core vesicles and multivesicular bodies.[43] In *C. elegans*, mutations in *unc-51* and *unc-14* resulted in abnormal localization of the axon guidance netrin receptor in neuronal cell bodies and abnormal axonal growth, further consistent with a role for Atg1 activity in the regulation of axonal morphology.[44] In mammals, mutations in *unc-51*/Ulk1/Atg1 homologues disrupted neurite formation/extension in mouse cerebral granule cells, and increased branching in cultured dorsal root ganglion neurons.[45] Although these phenotypes could be due to abnormal localization of axon guidance receptors or deficits in axonal transport, changes in lysosomal degradation may also play a role.

Neurite alteration via autophagy could also be mediated by changes in AV-lysosomal fusion. For example, overexpression of the N-terminal region of TI-VAMP/VAMP7, a v-SNARE found on late endosomes necessary for amphisome fusion with the lysosome,[46] disrupts axonal and dendritic outgrowth in mouse hippocampal neurons.[45] While AV induction in these animals may be normal, fusion and consequently degradation is disturbed, leading to defective neuritic morphology.

Multiple means of autophagy regulation converge on the covalent lipidation of microtubule-associated protein 1 light chain 3 (LC3), which converts the protein to the AV-associated membrane component LC3-II. Such a step has been recently implicated in neurite outgrowth and retraction,[23] so that protein kinase A-mediated LC3 phosphorylation suppressed AV formation and blocks neurite retraction, while rapamycin or neuronal stress enhances LC3 phosphorylation, AV formation, and neurite retraction.

Characterizing a role for constitutive autophagy in regulating CNS synaptic transmission and plasticity has become more straightforward with experiments using conditional autophagy-deficient mice. The use of "floxed" genetic technology allows particular sets of neurons to be autophagy deficient. For example, autophagy deficiency selectively in mouse Purkinje cells leads to axonal, but not dendritic, dystrophy and accumulation of aberrant membrane structures,[30] suggesting that constitutive autophagy is necessary for normal axonal morphology. In our recent studies, we find that DA neurons deficient in autophagy display larger presynaptic terminals and enhanced evoked DA release. Rapamycin induced AV formation in wild type, but not autophagy-deficient, DA synaptic

terminals, resulting in a decrease in presynaptic terminal volume (Hernandez and Sulzer, under submission).

Together, current data suggest that autophagy at synaptic terminals can degrade synaptic components. It may be that low levels or lack of autophagy initially results in synaptic or neuronal overgrowth, but that with continued autophagy deficiency, there may be an accumulation of damaged mitochondria and other cellular constituents that lead to synaptic loss.

TURNOVER OF PRESYNAPTIC COMPONENTS BY MACROAUTOPHAGY

In 1971, Eric Holtzman and colleagues reported that recycling synaptic vesicles at the lobster NMJ can fuse with multivesicular bodies and lysosomes, suggesting a means for normal synaptic vesicle degradation.[47] Thus, the neuron can control the fate of synaptic vesicle membrane following fusion so that, following reaccumulation into coated vesicles or endosomes, vesicle membrane can either be used to reform synaptic vesicles or be degraded. These studies also introduced an important point about neuronal autophagy: in many cases, neuronal AVs appear to function as so-called "amphisomes", meaning they are derived from both autophagic organelles and components of endosomes, in this case containing both endocytosed synaptic vesicle membrane and associated proteins.

The means by which recycling synaptic vesicle membrane can be differentially targeted to the lysosome are unknown. The adaptor proteins AP2 and AP3 can be selectively used for the recovery of fused synaptic vesicle membrane from the plasma membrane depending on neuronal activity, with AP3 providing bulk endocytosis with high activity levels.[48,49] These AP3-dependent endosomes may provide a structure that can donate the membrane to AVs or lysosomes. This suggests the presence of an early step that determines whether synaptic vesicle membrane is recycled or degraded (Figure 1). Another potential regulatory step for synaptic vesicle degradation is provided by Rab5, which both regulates endosomal function and vesicle recycling[50] and inhibits mTORC1 function,[51] which enhances macroautophagy.[52–54]

There are already thus several candidates that may determine how neuronal activity could provide selective degradation of presynaptic elements and organelles, including synaptic vesicles, mitochondria, endoplasmic reticulum, cytoskeletal elements, presynaptic receptors and channels, and endosomes. An important role for the appropriate localization of presynaptic mitochondria is particularly demonstrated in the modulation of synaptic strength due to effects on the availability of synaptic vesicles for fusion under periods of intense stimulus.[55]

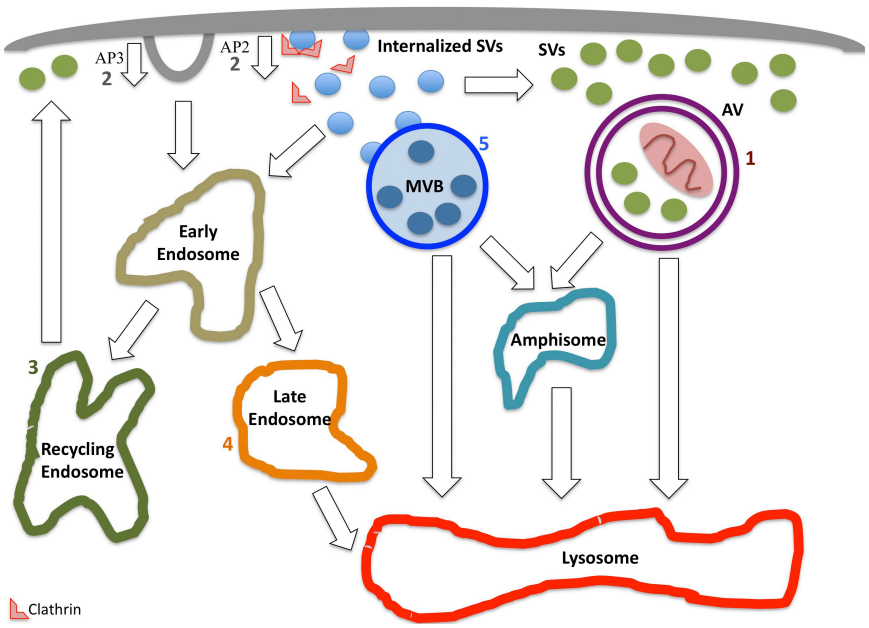


Figure 1. Proposed synaptic vesicle recycling and degradation pathways. AVs may directly sequester cytosolic synaptic vesicles and provide a system to deliver these organelles to lysosomes for degradation (1). In addition, for those synaptic vesicles that undergo full fusion with the plasma membrane, synaptic vesicle membrane can be internalized and targeted either for recycling or degradation. The adaptor proteins AP2 or AP3 mediate recovery of vesicle membrane, depending on the level of neuronal activity. AP2-mediated SV internalization involves clathrin-dependent endocytosis, for presumed uncaging and recycling (2), while AP3-mediated internalization involves an endosomal intermediate, from which membrane can either enter the recycling endosome to reform SVs (3), or a later stage endosome (4), Later stage endosomes may fuse with local AVs/amphisomes for transport to mature lysosomes where vesicular membranes are degraded. Following internalization, apparent synaptic vesicles are also observed within multivesicular bodies (MVBs) (5), which can subsequently fuse with an AV/amphisome or directly with the lysosome.

Recent evidence indicating autophagic degradation of synaptic vesicles is observed in dopaminergic neurons, for which the probability of neurotransmitter release appears to be related in part to the size of the readily releasable pool.[56] We observed a decrease in the number of synaptic vesicles following macroautophagy induction by rapamycin in striatum (Hernandez and Sulzer, under submission). Cyclic voltammetry recordings [57] show a decrease in evoked dopamine release from striatal terminals following macroautophagy induction. This response was absent in conditional autophagy-deficient dopaminergic neurons, consistent with a relatively rapid induction of autophagic synaptic vesicle

degradation. The data also suggest that rapamycin may decrease the number of presynaptic mitochondria, which as mentioned is implicated in modulating synaptic vesicle pools.

TURNOVER OF POSTSYNAPTIC RECEPTORS BY MACROAUTOPHAGY

GABA Receptors

In a study of the *C. elegans* NMJ, Bruce Bamber and colleagues identified a role for selective macroautophagy in the degradation of $GABA_A$ receptors (GABAR).[38] They disrupted expression of the netrin receptor, which is required for axon pathfinding, in GABAergic or cholinergic neurons, or both. Loss of GABAergic innervation decreased GABAR clustering. When muscle cells were completely denervated, GABARs accumulated in AVs via endocystosis. When autophagy was blocked by a UNC-51 mutation, the decrease in GABA-mediated currents was rescued. These data suggest that receptor accumulation in AVs is inhibited by contact, rather than function, of presynaptic inputs. Remarkably, these results were specific for GABARs, as when the netrin receptor was selectively deleted from cholinergic inputs, neither accumulation of acetylcholine receptors in AVs nor a decrease in currents evoked by cholinergic agonists was observed. The authors suggest that innervation provides an intercellular signal independent of neurotransmitter release that regulates receptor localization and blocks degradation of GABARs through macroautophagy.[38] This is consistent with Hollenbeck's earlier suggestion that neurons regulate autophagy to degrade synaptic components depending on their physiological state.[47]

Additional studies suggest further crosstalk between the biochemical systems that regulate autophagy and GABAergic signaling. The GABAA receptor-associated protein (GABARAP), a homolog of atg8/LC3, an autophagy-related protein found on the outer and inner AV membranes, is involved in GABAR trafficking from the Golgi apparatus to the plasma membrane,[58,59] autophagy induction, AV maturation, and clearance of mitochondria.[60,61] Like atg8 and its mammalian homologue, LC3, unlipidated GABARAP is cytosolic, but its localization changes to AV membranes following lipidation.[58,59] During extinction of fear conditioning, GABARAP activity is necessary for NMDA-dependent insertion of GABARs into the postsynaptic membrane in hippocampal CA1 neurons, indicating a function in strengthening inhibitory synapses during learning and memory.[62]

Glutamate receptor activation has also been reported to target $GABA_B$ receptors to lysosomes in cortical neurons in a calcium-dependent manner,[63] reminiscent of calcium-regulated stress response induction of autophagy as discussed above.

More broadly, the state of phosphorylation and ubiquitination, beta-arrestins, and interaction with adaptor proteins can each regulate endocytosis[64] and subsequent trafficking of neurotransmitter receptors for recycling or degradation. Rab5[49,51,65] or VAMP7[46] activity may be required for receptor targeting to amphisomes/lysosomes for degradation. Additional candidates have been introduced in experiments in yeast, including the "endosomal sorting complex required for transport" (ESCRT) signals introduced by Scott Emr and collaborators.[66,67]

Glutamate Receptors

There is also evidence for autophagic turnover of glutamate receptors. While to our knowledge, AMPAR accumulation in AVs has not yet been shown to affect synaptic transmission, it is well established that a net decrease in the number of surface postsynaptic AMPARs results in LTD expression.[32] Moreover, NMDAR activation can induce AMPAR internalization followed by degradation in the lysosome, with lysosomal protease but not proteasome inhibitors inhibiting the loss of AMPARs in hippocampal neurons.

Hippocampal neurons and Purkinje cells of mice carrying a null mutation for the beta subunit of the adaptor protein AP4, which is involved in basolateral sorting in epithelial cells and in neurons and associates with lysosomal associated protein 2 (LAMP2),[68] exhibit axonal swellings and an accumulation of axonal AVs. To study the effect of this AP4 mutation on protein sorting, Matsuda and colleagues focused on Purkinje cells because their dendrites, which project to the molecular layer of the cerebellum, are spatially separated from their axon, which extends into the deep cerebellar nuclei (DCN).[69] AMPARs are normally localized to dendritic spines, but Purkinje cell axons from mice lacking the beta subunit of AP4 were immunolabeled for AMPARs both *in vivo* and *in vitro*, indicating receptor mislocalization. Improper targeting of AMPARs to axons was mediated by a lack of interaction between AP4 and transmembrane AMPA receptor regulatory proteins (TARPs). Electron microscopy indicated that the bulging regions of axons from AP4 null mutant mice contained AV-like organelles. Occasionally these structures were found at axon terminals that appeared normal and formed synapses with DCN neurons. AP4 mutant mice exhibited an

increase in the lipidated, AV-membrane bound form of LC3, LC3-II, and AMPARs co-localized with GFP-LC3 puncta in axons of Purkinje cells *in vivo* and in hippocampal cells *in vitro*,[69] indicating AMPAR accumulation in axonal and terminal AVs.

Reminiscent of autophagy of GABARs discussed above, the effects were specific to AMPARs, as the metabotrophic glutamate receptor 1 (mGLUR1) was not found in axons in Purkinje cells axons *in vivo* nor in hippocampal neurons *in vitro*,[69] and the lack of AP4 did not affect localization of vesicle-associated membrane protein 2/synaptobrevin II (VAMP2), part of the SNARE complex,[70] nor the NR1 subunit of the NMDAR.

This delivery AMPAR to lysosomes may be dependent on subunit composition, as GluR1 preferentially enters the recycling pathway following activation with AMPA, whereas GluR2 and GluR1/GluR2 heterodimers are trafficked to the late endosome/lysosome for degradation following activation with NMDA.[71] Sorting of AMPAR subunits between the recycling and lysosomal pathways is driven by the interaction of subunit cytoplasmic tails with NSF, suggesting that such interactions may provide a mechanism for the selective degradation of synaptic receptors through autophagy (Figure 2).

This fate depends on the mode of activation and AMPAR subunit composition. After AMPA-mediated internalization, GluR2 subunits enter the recycling pathway, but following activation with NMDA, they are targeted for lysosomal degradation. Glur1 enters the recycling pathway and GluR3 is trafficked to the lysosome, regardless of NMDAR activation. NSF interaction with the GluR2 cytoplasmic tail is implicated in determining whether GluR2 receptors enter the recycling or lysosomal degradation pathway, while GluR3, which lacks an NSF-binding domain, is preferentially trafficked to the lysosome. Thus, subunit-specific interactions with adaptor proteins have profound effects on receptor degradation. These interactions may also differ depending on whether delivery to the lysosome is via macroautophagy or multivesicular bodies.

While it is likely that receptors, transporters, and channels can be degraded by autophagy, the mechanisms controlling degradation may be different for specific components. This could entail early regulatory steps: for example, AP3 and its adaptor complex regulator AGAP1 enable the recycling of endocytosed m5 muscarinic receptors in DA neurons,[72] which in turn regulates the level of evoked DA release. Thus, AP3/AGAP1 activity could target m5 muscarinic receptors in DA neurons for degradation without loss of other synaptic receptors or channels. Uncovering these processes is complicated by the strong possibility that degradation requires accumulation of membrane-associated

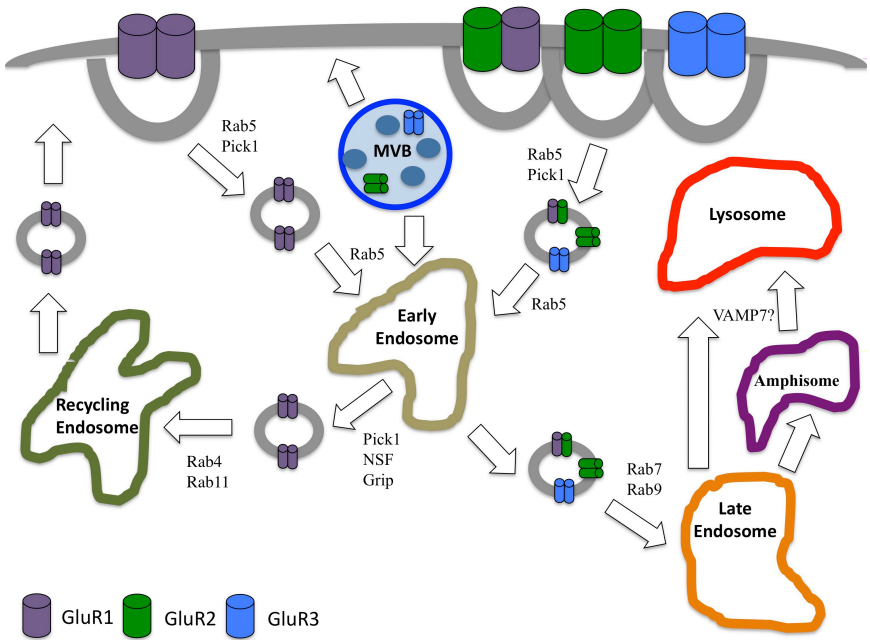


Figure 2. Model of AMPA receptor recycling and degradation. The fate of endocytosed receptors, either to be recycled to the cell surface or degraded, impacts synaptic function. Following LTP induction, AMPARs are inserted into the postsynaptic membrane, while following LTD induction, AMPARs are internalized via clathrin-dependent endocytosis. Upon internalization, receptors are first trafficked to the early endosome, which requires PICK1 and Rab5 activity. In the early endosome, internalized receptors are associated with Rab4 and Rab5. PICK1 and Grip are though to facilitate AMPAR recycling. If trafficked to the recycling endosome, receptors become associated with Rab4 and Rab11; if trafficked to the late endosome, they become associated with Rab7 and Rab9.

proteins in multivesicular bodies rather than AVs, a topic little explored in the CNS to date.

SUMMARY

After decades in obscurity, the field of neuroscience has revisited Hollenbeck's and Bunge's pioneering work indicating that autophagy plays roles in trafficking membrane to and from the synapse, with consequences that regulate structure, excitation/inhibition balance at synapses, synaptic morphology, and synaptic transmission. While we are now in preliminary stages of characterizing these phenomena, they appear to be related to selective autophagy of synaptic constituents. Thus, in addition to macroautophagy's well-established roles in stress

response and cellular homeostasis as addressed throughout this volume, data presented here suggest that synaptic terminals utilize this anciently conserved process as a means of modulating neurotransmitter release and synaptic plasticity. From this perspective, autophagic processes resemble other fundamental biological phenomena that were adopted by the nervous system to provide means to provide synapses with a wide range of states.

The observations on autophagic targeting of GABARs and AMPARs have important implications for the roles of autophagy in synaptic function under nominally unstressed conditions.[38,69] First, they indicate that presynaptic GABAergic contact provides an intercellular signal postsynaptically that may be independent of neurotransmitter release to regulate receptor localization and blocked degradation of GABARs through autophagy.[38] Second, they suggest that particular types of synaptic receptors may be selectively degraded through autophagy within the same cellular compartment, apparently in part due to particular interactions with adaptor proteins.[38,69,71]

Perhaps most importantly, these findings point towards a general role for autophagy in regulating synaptic plasticity. For example, GABA and acetylcholine receptors are inhibitory and excitatory at the *C. elegans* NMJ, and so selective degradation of inhibitory GABARs can alter the balance between excitatory and inhibitory signals at these synapses. Such regulation is important in circuits where the balance between excitation and inhibition alters plasticity, such as in the visual system, which relies on GABAergic signaling during development of ocular dominance columns[73,74] or the corticostriatal synapse, where either long term depression or potentiation can be induced depending on spike timing.[75] Thus, crosstalk between trafficking molecules and the autophagy pathway might result in changes in synaptic plasticity [51,71] and a major future issue will be to determine how synaptic components are differentially targeted for recycling or lysosomal degradation.

While the mechanisms of synaptic autophagy are incompletely defined at present, many other signaling pathways and mechanisms identified in other cell types have been subsequently found to be adapted in complex ways in the nervous system, and there is no reason to presume that lysosomal degradative pathways will provide an exception to this observation.

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