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·Review·

Autophagy in synaptic development, function, and pathology

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In the nervous system, neurons contact each other to form neuronal circuits and drive behavior, relying heavily on synaptic connections. The proper development and growth of synapses allows functional transmission of electrical information between neurons or between neurons and muscle fibers. Defects in synapse-formation or development lead to many diseases. Autophagy, a major determinant of protein turnover, is an essential process that takes place in developing synapses. During the induction of autophagy, proteins and cytoplasmic components are encapsulated in autophagosomes, which fuse with lysosomes to form autolysosomes. The cargoes are subsequently degraded and recycled. However, aberrant autophagic activity may lead to synaptic dysfunction, which is a common pathological characteristic in several disorders. Here, we review the current understanding of autophagy in regulating synaptic development and function. In addition, autophagy-related synaptic dysfunction in human diseases is also summarized.

Keywords: autophagy; synaptogenesis; synaptic elimination; synaptic function; synaptic pathology

Introduction

As the predominant form of autophagy, macroautophagy (hereafter “autophagy” for short) is an essential self-defense mechanism for the maintenance of cellular homeostasis. It operates by the sequestration of cytoplasmic materials and proteins into a double-membrane autophagosome, which fuses with a lysosome or late endosome whereby encapsulated materials are degraded. Under pathological conditions, autophagy functions as a critical quality-control system; damaged intracellular organelles, misfolded proteins, or protein aggregates are removed by autophagic clearance.

Maday and Holzbaur were the first to uncover the biogenesis of autophagosomes in neurons[1]. Under physiological conditions, autophagosomes are generated in a compartmentalized pattern, as most are synthesized in the axonal terminals[1]. Although both anterograde-directed motor kinesin and retrograde-directed motor dynein are tightly associated with axonal autophagosomes[2, 3], binding of the scaffolding protein JIP1 to the autophagosome adaptor LC3 ensures the robust retrograde transport of newly-formed autophagosomes along microtubules in axons[4]. Emerging lines of evidence suggest that autophagy regulates the development and function of axons, dendrites, and synapses. Besides, insufficient or excessive neuronal autophagy contributes to pathological changes in these polarized structures. The regulatory role of autophagy in axonal and dendritic degeneration was discussed in our previous review[5].

Synapses are dynamically organized elements[6]; the wiring and rewiring of neuronal circuits largely depend on orchestrated changes in the strengths of synaptic contacts in response to developmental and environmental cues. The synapse is the point of contact between the neurons, and plays a crucial role in the transmission of neuronal information. The integrity of synaptic structure and function is pivotal to ensuring that neurons acquire, transfer, process, and store information smoothly and systematically. Because of the high energy demand and protein turnover

ratio in the region of the synapse, the timely clearance of synaptic contents appears to be crucial for maintaining synaptic function[7]. Several lines of evidence point to the involvement of autophagy in synaptogenesis, synaptic elimination, and synaptic transmission. Besides, autophagy-related synaptic dysfunction has been implicated in neurodevelopmental disorders and neurodegenerative disorders. In this article, we review the recent experimental findings on how autophagy modulates the development, function, and pathology of the synapse.

Autophagy in Synaptic Development

Synapses are highly dynamic components of neurons, and persistent turnover of synapses occurs during development and in the adult brain. During development, the synaptogenesis and synaptic elimination are under delicate balance to maintain the normal functions of neuronal circuits[8-10]. Synaptic gain and elimination, proceeding by synaptic turnover, are key rearrangement events in learning, memory, and cognition[11]. Since the autophagic pathway plays a fundamental role in regulating protein turnover, we summarize the recent progress in understanding the regulatory effects of autophagy on synaptogenesis and synaptic elimination.

Autophagy in Synaptogenesis

Each individual *Drosophila* neuromuscular junction (NMJ) contains hundreds of synapses and therefore is a well-established model system for studying synaptogenesis. Synaptogenesis is a multistep process, and a variety of molecules and signaling pathways have been identified to mediate early synaptogenesis[12]. Autophagy and the ubiquitin-proteasome system are major pathways for protein degradation in cells. Accumulating evidence has indicated the importance of protein degradation *via* the ubiquitin-proteasome system, which is mainly responsible for the turnover of short-lived cytosolic proteins, in regulating synaptic growth[13-16]. Highwire (Hiw), an E3 ubiquitin ligase that mediates key steps in the protein ubiquitination process, negatively governs synaptic growth at the *Drosophila* NMJ[17, 18]. It has been suggested that Hiw mediates presynaptic bone morphogenetic protein signaling through ubiquitination mechanisms and thereby controls the growth of neuromuscular synapses[19]. Recent studies have emphasized the involvement of autophagy, which is responsible for the degradation of long-lived proteins and damaged organelles, in synaptic development. Increased levels of the synaptic protein synaptotagmin 1 have been found along with upregulated autophagy proteins (Atg9a and LC3-II) during the differentiation of mouse neural stem cells[20]. Under transmission electron microscopy, autophagosomes are distributed in the synaptic terminals of cultured hippocampal neurons[21], indicating that autophagy is required during synaptogenesis.

In 2009, Shen and Ganetzky reported that autophagy plays a positive role in promoting the growth of the larval *D. melanogaster* NMJ[22]. Impaired autophagy significantly reduces the size of NMJ synapses and the number of boutons in larvae, whereas overexpression of the autophagy-associated gene *atg1* induces NMJ overgrowth by elevating autophagic activity[22]. In accordance with these results, Batlevi *et al.* also reported a decreased number of synaptic boutons in dynein light chain 1 (*ddlc1*) mutant *Drosophila* that exhibited attenuated autophagic activity and reduced protein clearance[23].

Although the molecular mechanism underlying autophagy-regulated synaptic growth is not entirely clear, it has been suggested that autophagy regulates NMJ growth by inducing the degradation of Hiw[22]. *D. melanogaster* Rae1, an Hiw cofactor, binds to Hiw and prevents its autophagy-regulated downregulation[24]. In addition, the mitogen-activated protein kinase signaling pathway also participates in autophagy-mediated synaptogenesis. The downstream signaling cascades of this pathway, including extracellular signal-regulated kinase (ERK), c-Jun-N-terminal kinase (JNK), and p38 mitogen activated kinase, are well-characterized mediators of synaptic development[25]. Wairkar *et al.* revealed that Unc-51, the *Caenorhabditis elegans* Atg1 ortholog, promotes synaptic formation and development by downregulating ERK signaling[26]. JNK and its transcriptional effector AP-1 can be activated in response to oxidative stress. The activation of JNK/AP-1 regulates synaptic development under oxidative stress by activating autophagy[25, 27, 28].

Autophagy in Synaptic Elimination

It is worthy of note that the phenomenon of increased synapse number can result from enhanced synaptic formation or decreased synaptic elimination. Synaptic elimination, also known as synaptic pruning, is the process of removing redundant or inappropriate synaptic connections. Synaptic elimination helps to fine-tune precise

neuronal connectivity and is as important as synaptogenesis during brain development[29].

The spine is a specialized postsynaptic protrusion on dendrites. The time course of spine development in primary cultured hippocampal neurons is similar to that of dendritic spines in mouse brain[30, 31]. In cultured neurons, the number of spines increases during 6–10 days *in vitro* (DIV), peaks at 14–21 DIV, and decreases after 21–28 DIV[32]. Tang *et al.* found that silencing the key autophagy gene *atg7* increases the spine density at 19–20 DIV[32]. Interestingly, unlike control cells in which the rates of synapse formation and elimination are approximately equivalent, hippocampal neurons deficient in *atg7* exhibit normal spine formation but greatly inhibited elimination, indicating that autophagy enables synaptic elimination in cultured hippocampal neurons during the "mature" developmental stage[32, 33]. On the other hand, deficits in autophagy leading to insufficient synaptic elimination are closely associated with several neurodevelopmental diseases that are discussed in detail below. As autophagy is required for development of the *Drosophila* NMJ, the normal spine formation in atg7-deficient cultured neurons might be due to species differences or the different conditions between *in vivo* and *in vitro* studies.

Autophagy in Synaptic Function

In neurons, the majority of autophagosomes are locally synthesized in the distal terminals of axons[3] (Fig. 1A). After generation, autophagosomes are transported towards the soma and the engulfed cytoplasmic materials are delivered to lysosomes for degradation[4, 5]. Although the molecular mechanism involved in the biosynthesis of neuronal

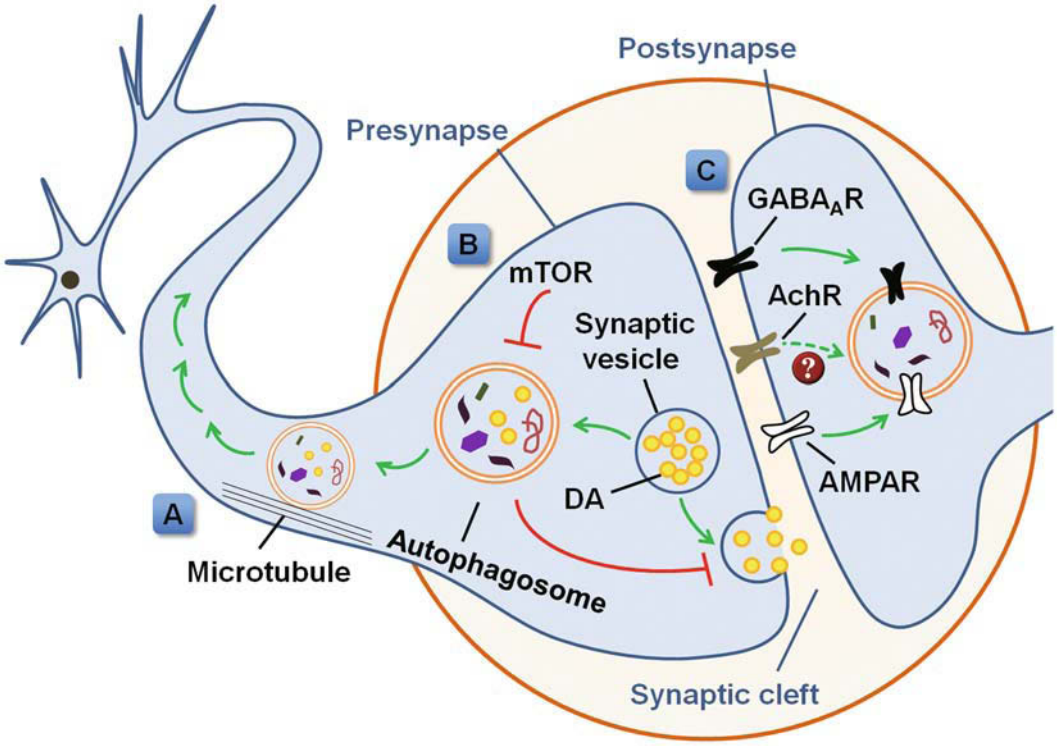

Fig. 1. Regulatory role of autophagy in synaptic terminals. (A) Cytoplasmic contents, including misfolded proteins and organelles, are engulfed into double-membrane autophagosomes. Most of the autophagosomes are locally synthesized in axons and are then transported along microtubules towards the cell body. (B) In the presynaptic terminals of dopaminergic neurons, autophagy mediates synaptic vesicle degradation and suppresses DA release. mTOR negatively regulates autophagic activation. (C) In postsynaptic terminals, autophagy contributes to the degradation of postsynaptic receptors, such as GABA$_A$Rs and AMPARs. Whether or not autophagy governs AChR degradation is unclear. AChR, acetylcholine receptor; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-type glutamate receptor; DA, dopamine; GABA$_A$R, gamma-aminobutyric acid-A receptor; mTOR, mammalian target of rapamycin.

autophagosomes is not entirely understood, accumulating evidence indicates that the Rab family and related small GTPases are required for the formation and maturation of autophagosomes[34]. A recent study further showed that the GTPase Rab26 directs synaptic vesicles towards pre-autophagosomal structures[35], implying that autophagy participates in synaptic transmission. Synaptic transmission relies on neurotransmitters and their receptors. In this process, neurotransmitters are initially released from the presynaptic terminals, and subsequently bind to and activate their receptors located on the postsynaptic terminals, triggering a series of biochemical reactions.

A growing body of evidence has revealed that autophagy is capable of regulating synaptic function in presynaptic and postsynaptic terminals (Fig. 1B, C). Both basal and induced autophagy participate in the modulation of synaptic transmission and plastic remodeling. Autophagy-regulated synaptic function in GABAergic, dopaminergic, glutamatergic, and cholinergic neurotransmitter systems has been described in detail (Table 1).

Table 1. Autophagy-regulated synaptic function in GABAergic, dopaminergic, glutamatergic, and cholinergic neurotransmitter systems

Neurotransmitter system	Species	Tissues/Cells	Description	Reference
GABAergic	*C. elegans*	Non-innervated muscle cells	$GABA_A$ receptors target to autophagosomes for degradation	[49]
Dopaminergic	*Mus musculus*	DA neurons from DAT Cre mice	Autophagy activation depresses evoked DA secretion in dopaminergic neurons	[40]
	M. musculus	METH-treated ventral midbrain DA neurons	Perturbed DA release may in turn trigger autophagy	[45]
Glutamatergic	*Rattus norvegicus*	Primary cultured hippocampal neurons exposed to KCl	NMDAR-dependent autophagy contributes to AMPAR degradation	[52]
Cholinergic	*M. musculus*	Tibialis anterior muscle	Autophagy regulates the basal and atrophy-induced turnover of CHRN	[53]
	C. elegans	Non-innervated muscle cells	AChRs do not traffic to autophagosomes	[49]

AChRs, acetylcholine receptors; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-type glutamate receptor; DA, dopamine; CHRN, muscle-type cholinergic receptor, nicotinic/nicotinic AChR; DAT, dopamine transporter; KCl, potassium chloride; METH, methamphetamine; NMDAR, glutamatergic N-methyl-*D*-aspartate receptor.

Autophagy in Presynaptic Terminals

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase that acts as a key cell growth mediator *via* integrating the inputs from multiple upstream signals[36, 37]. mTOR blocks the activation of autophagy at an initial step during autophagosome formation[38]. Notably, mTOR regulates local RNA translation at the synapse and thus appears to be important for the synthesis of synaptic proteins[39]. Emerging lines of evidence highlight the crucial role of the mTOR signal in regulating synaptic transmission[40, 41] and synaptic plasticity[42]. Inhibition of the mTOR signaling pathway by rapamycin, which upregulates autophagic activity in mammalian cells, reduces the numbers of synaptic vesicle and depresses the evoked dopamine (DA) secretion from dopaminergic neurons[40] (Fig. 1B). Mice deficient in DA neuron-specific autophagy (*atg7* DAT Cre) exhibit enhanced DA release in response to stimulation and an increased rate of synaptic recovery[40]. Based on these findings, it has been speculated that autophagy acts as a brake on presynaptic activity by regulating the kinetics of DA release[43]. The perturbed neurotransmitter release may in turn trigger autophagy induction. For instance, dopaminergic terminals

are particularly vulnerable to methamphetamine (METH), a widely-abused psychostimulant[44]. In ventral midbrain DA neurons, METH promotes DA synthesis and subsequently elevates the cytosolic DA level[45]. The excessive DA metabolites may lead to the generation of damaged lipids and proteins, thereby inducing autophagic degradation[45].

Autophagy in Postsynaptic Terminals

In postsynaptic terminals, autophagy contributes to the degradation of special types of receptors. γ-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter in the central nervous system (CNS). $GABA_A$ receptors ($GABA_A$Rs), the major postsynaptic components of GABAergic synapses, mediate fast synaptic inhibition in the brain[46]. These receptors, composed of different subunits, are distributed at both synaptic and extra-synaptic sites, where they play crucial roles in governing phasic and tonic inhibition, respectively[47, 48]. *C. elegans* is an ideal animal model for investigating neurotransmitter receptors because it can be genetically manipulated. In 2006, Rowland *et al.* for the first time reported that the cell-surface $GABA_A$Rs, but not acetylcholine receptors, targeted to autophagosomes for degradation[49] (Fig. 1C). In contrast to the simple and uniform distribution of $GABA_A$Rs in *C. elegans*[50], the structure of $GABA_A$Rs is rather complex in mammalian cells[51], and there is still no evidence that autophagy is required for the turnover of $GABA_A$Rs in mammalian cells.

In addition to GABARs, glutamatergic N-methyl-*D*-aspartate receptor (NMDAR)-dependent autophagy contributes to the degradation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-type glutamate receptors (AMPARs) in cultured rat hippocampal neurons upon stimulation (Fig. 1C), suggesting that autophagy participates in NMDAR-dependent synaptic remodeling[52].

The regulatory effect of autophagy on cholinergic neurons has not yet been fully clarified (Fig. 1C). Rowland *et al.* showed that acetylcholine receptors do not traffic to autophagosomes in the non-innervated muscle cells of *C. elegans*[49]. In contrast, a recent report demonstrated that in mouse tibialis anterior muscles, autophagy contributes to the basal and atrophy-induced turnover of muscle-type cholinergic receptors, nicotinic/nicotinic acetylcholine receptors in a tripartite motif containing 63 (TRIM63)-dependent manner[53]. Such a discrepancy might be due to the different species used in experiments. Nevertheless, autophagy seems to act as a universal regulator for modulating receptor turnover in postsynaptic terminals, though the substrate-specificity of autophagosomes still needs to be well defined.

Autophagy and Synaptic Regulators

Despite the uncertainty of an association between synaptic regulators and autophagy, defects in certain synaptic proteins result in the failure of either autophagic induction or autophagic clearance. For example, loss of neuron-specific synaptic v-SNARE (soluble NSF attachment protein receptor) *n-syb* (*neuronal Synaptobrevin*) leads to increased autophagic activity in adult *D. melanogaster* photoreceptor neurons[54]. Such enhancement of autophagy is proposed to be a consequence of primary vesicle trafficking defects[54]. Snapin, initially identified as a neuronal SNARE-binding protein, is a crucial modulator of vesicle release and presynaptic homeostatic plasticity[55, 56]. Deleting *snapin* promotes the accumulation of autolysosomes in cortical neurons by impairing efficient autophagic turnover[57]. Therefore, synaptic regulators in turn may affect the autophagy-lysosomal degradative system.

Involvement of Autophagy in Synaptic Pathology

Functional autophagy participates in a variety of events in synapses, including dendritic spine elimination (Fig. 2A), local protein clearance and turnover (Fig. 2B), and synaptic growth. Morphological and functional impairment of synapse is a common theme in the pathogenesis of many neurological diseases. However, the potential impact of autophagy on synaptic pathology has not yet been explored in all neurological diseases. Here, we discuss the recent evidence supporting a role of autophagy in mediating synaptic pathology in human diseases, including neurodevelopmental disorders (e.g. autism spectrum disorders [ASDs]) and neurodegenerative disorders (e.g. Alzheimer's disease [AD][58, 59] and Parkinson's disease [PD][60, 61]). Moreover, the involvement of autophagy has also been noted in synaptic dysfunction upon aging and the burden of oxidative stress (OS), a condition involved in several neurological diseases.

Neurodevelopmental Disorders

Appropriate elimination of synapses is a crucial step for neuronal network refinement during brain development, while insufficient or abnormal synaptic elimination is linked to many neurodevelopmental disorders. ASD

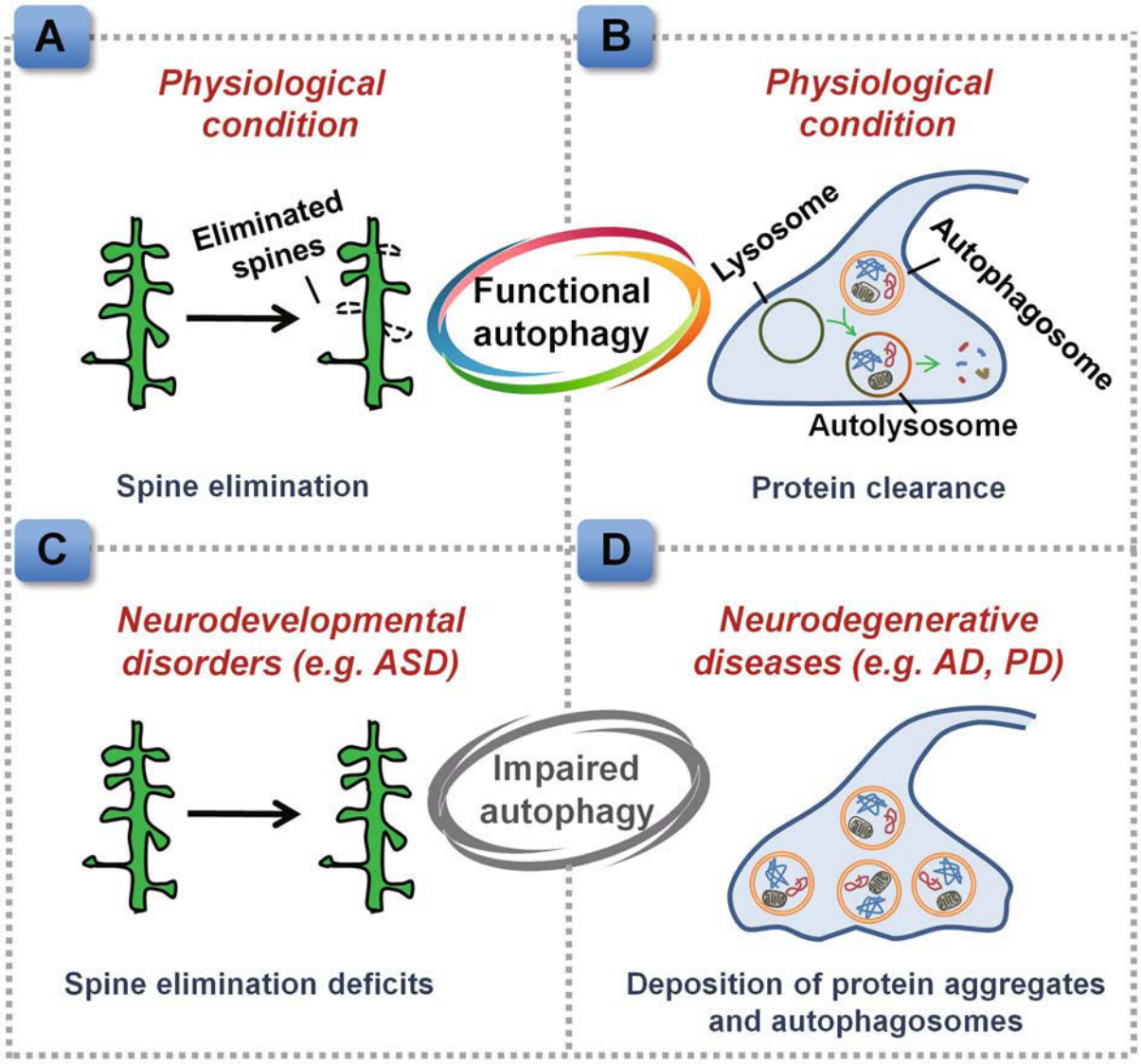

Fig. 2. Autophagy-related synaptic pathology in neurological diseases. Functional autophagy participates in dendritic spine elimination (A) and local protein clearance in the synapse (B). Impaired autophagy leads to spine elimination deficits in neurodevelopmental disorders, such as ASD (C). In addition, insufficient protein clearance caused by abnormal autophagy leads to the deposition of aberrant or misfolded protein aggregates and autophagosomes in synapses, which is a pathological feature of several neurodegenerative diseases such as AD and PD (D). AD, Alzheimer's disease; ASD, autism spectrum disorder; PD, Parkinson's disease.

is characterized by deficits in social interaction and communication, restricted interests, and repetitive behaviors, and the aberrant development and function of synapses is known to be involved in its pathogenesis[62]. Compared to age-matched control cases, increased dendritic spine densities occur in the frontal, temporal, and parietal lobe regions of ASD brains[63], and the greater spine densities are correlated with reduced cognitive function in individuals with ASD[63]. In addition, the increased dendritic spine density is predominantly caused by reduced developmental spine elimination. Most importantly, such spine pruning deficits result from hyperactivation of the mTOR signaling pathway and impaired autophagy[32]. Although the molecular mechanism by which autophagy

contributes to synaptic regulation has not yet been fully clarified, a recent report identified a key gene involved in this process. Ambra1 is a prominent upstream regulator of Beclin 1 (a principal mediator of autophagosome formation). Deficiency in Ambra1 results in autism-like phenotypes in female mice[64], implying that deregulation of the autophagic pathway causes the pathology of autism. Based on this evidence, it is possible that dysfunctional autophagy tends to contribute to synaptic pathology and leads to ASD phenotypes (Fig. 2C), while activation of autophagy may normalize the dendritic spine elimination and correct the synaptic pathology in ASD.

Neurodegenerative Diseases

In neurodegenerative diseases, synaptic loss and dysfunction commonly occurs before that in the soma. Besides, the formation and accumulation of aberrant or misfolded protein aggregates, owing to insufficient protein clearance by autophagy or other intracellular degradative pathways, is another pathological feature of neurodegenerative disorders[65]. There is no doubt that dysfunctional protein turnover in synapses is associated with the pathological protein accumulation. Indeed, excessive protein aggregates as well as autophagic vacuoles have been noted to accumulate locally in synapses.

Synaptic dysfunction is highly correlated with the cognition and memory decline in age-related neurobiological changes such as AD[66, 67]. In young AD mice (4–6-month-old PS1/APP mice), increased accumulation of autophagic vacuoles is correlated with aberrant presynaptic terminals[68]. In accord with this finding, senescence-accelerated prone 8 (SAMP8) mice, another AD model, exhibit elevated numbers of LC-3 positive cells in the hippocampus as well as prominent synaptic loss[69]. Generally, increased formation of autophagic vacuoles results either from induced autophagic activity or from autophagic flux defects. In primary cultured neurons with AD-like injury and in AD animal models, autophagy has been demonstrated to act as a protective mechanism, as the stimulation of autophagy or the recovery of lysosomal proteolysis is able to prevent AD-like neuritic degeneration, possibly by promoting the maturation of autophagosomes[5, 70]. In view of this point, we speculate that the accumulation of autophagic vacuoles, most likely caused by defective degradation of synaptic proteins (Fig. 2D), matches the synaptic dysfunction in AD and contributes to the cognitive and memory deficits in patients. This hypothesis is supported by a recent finding that oleuropein aglycone protects against pyroglutamylated-3 amyloid β peptide toxicity and synaptic dysfunction by activating neuronal autophagic machinery as determined by elevated Beclin 1 and LC3 immunoreactivity along with enhanced degradation of autophagy substrates[71].

PD is characterized by the accumulation of the aggregation-prone protein α-synuclein, which, under physiological conditions, functions in modulation of the presynaptic neurotransmitter vesicle pools[72, 73]. Wild-type α-synuclein is normally degraded by chaperone-mediated autophagy, another essential type of autophagy in which a pool of cytosolic proteins are targeted to lysosomes by chaperones for degradation[74, 75]. Macroautophagy is thought to be a compensatory mechanism for the failure of chaperone-mediated autophagy, and defective autophagy enhances the deposition of aberrant α-synuclein aggregation in Lewy bodies under the pathological conditions of PD[76]. The synapse is assumed to be the major target of α-synuclein, as aberrant α-synuclein deposition is found predominantly in presynaptic terminals and leads to synaptic pathology[77] (Fig. 2D). Impaired autophagic clearance results in the deposition of α-synuclein in presynaptic terminals of Atg7-deleted mice[78].

In addition to α-synuclein, a wealth of evidence highlights the importance of the mutations of another two PD gene products, leucine-rich repeat kinase-2 (LRRK2) and parkin, in synaptic pathology of PD[79, 80]. These PD gene products are involved in the maintenance of synaptic morphology and mediate synaptic protein trafficking. A detailed discussion of synaptic autophagy, LRRK2, and parkin in PD models can be found in another review[81]. Although the role of autophagy in the synaptic pathology of PD remains largely unexplored, it is known that parkin recruits damaged mitochondria for degradation through autophagic proteolysis. It is possible that impaired parkin may cause aberrant mitochondrial turnover regulated by selective autophagy (termed mitophagy), which contributes to abnormal synaptic homeostasis in PD[82].

Aging

The aging-associated reduction of synaptic number and function has been noted in the pathological changes in several neurodegenerative disorders; these changes

precede the memory impairment and cognitive decline in patients[83]. In addition, autophagic activity declines during aging, while autophagy augmented by genetic manipulation or by pharmacological interference (e.g. administration of rapamycin or spermidine) extends the lifespan of model organisms[84]. Studies of NMJ aging in *Drosophila* have revealed an abundant accumulation of early endosomes, multivesicular bodies, and autophagosomes in the synaptic boutons of old flies[85]. The enhanced autophagy might be closely associated with the misregulated recycling of synaptic vesicles in the motor terminals of old flies. Deficient autophagy in muscle leads to deterioration of neuromuscular synaptic function and precocious aging in mice[86]. Based on this evidence, it appears that age-related synaptic impairments are exacerbated by deficits in autophagy.

Oxidative Stress Burden

The cause of neuronal death in neurodegenerative diseases is known to be multifactorial, the OS burden caused by excessive generation of ROS being one of the most convincing theories of pathogenesis[87]. ROS not only leads to apoptotic cell death, but also regulates synaptic growth and function[28, 88]. Autophagy is the main cellular response to OS burden. In a *Drosophila* model of lysosomal storage disease, *spinster (spin)*, OS induces synaptic overgrowth[28]. Autophagy-related genes, such as *atg1* and *atg18*, are required for OS burden-triggered synaptic overgrowth in this model, and disturbance of autophagy is able to reverse synaptic overgrowth[28]. Therefore, it is hypothesized that upon OS burden, the overproduction of ROS may activate autophagy which plays a key role in mediating synaptic growth, function, and senescence[25]. Nevertheless, there is a lack of confirmatory data on the involvement of autophagy in regulating OS-induced synaptic pathology in mammalian cells. Owing to the importance of OS burden in a wide range of neurodegenerative disorders, a better understanding of the precise role of OS-activated autophagy in synaptic regulation may provide fundamental insights into pathogenesis and may offer novel targets for therapeutic interference.

In addition to the human disorders mentioned above, the impact of autophagy on synaptic pathology has also been addressed in other laboratory models of neurological diseases including ischemia[89], electroconvulsive seizures[90], and neurotoxicity[91].

Conclusions

Although in the past few years a wealth of evidence has been reported on this topic, the most crucial questions about how autophagy regulates synaptic development, function, and pathology have not yet been fully answered. Increased autophagy induction is found in synaptic terminals during pathogenesis. However, whether the excessive autophagy machinery is beneficial, harmful, or simply reflects an epiphenomenon, is yet to be finally determined. Hopefully, a clearer understanding of autophagy function in the physiological and pathological responses of synapses may open up new avenues for the development of therapeutic approaches targeting synaptic pathology in human disorders.

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