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Review Article

The Role of Synaptic Autophagy in Neurodegeneration: Mechanisms and Therapeutic Opportunities

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ABSTRACT

This review explores the critical role of synaptic autophagy in neurodegeneration, highlighting its mechanisms and potential therapeutic avenues. Neurons rely on synapses for efficient communication and information processing, with autophagy serving as a vital cellular process for maintaining synaptic integrity under various physiological conditions. The review discusses the different forms of autophagy, macroautophagy, microautophagy, and chaperone-mediated autophagy and their influence on synaptogenesis, synaptic elimination, and overall synaptic transmission. We examine the relationship between impaired autophagic activity and the pathogenesis of neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases, which are associated with decreased synaptic function due to disrupted protein turnover and organelle quality control. Furthermore, the involvement of key signaling pathways, including the mTOR pathway, in regulating autophagy and synaptic health is discussed. By elucidating the interplay between autophagy and synaptic dynamics, this review underscores the potential of targeting autophagy-related pathways as a therapeutic strategy in neurodegenerative diseases, offering insights into the mechanisms underlying synaptic dysfunction and the broader implications for neuronal health.

KEYWORDS: Synaptic autophagy, mTOR, Signaling pathways, Neurodegeneration

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1. Introduction

Many diseases are caused by defects in the development or formation of synapses, which are necessary for adequately transmitting electrical information between neurons, neurons, and muscle fibers. In the nervous system, neurons interact to form neuronal circuits and drive behavior, mainly through synaptic connections. In neurons, autophagy is amplified during low neuronal activity, sensory deprivation, and loss of neurotrophic factors that act indirectly through mTOR signaling or in response to amino acid starvation. Autophagy is a biologically conserved cellular mechanism for the breakdown and recycling of cellular components via the lysosomal pathway [1,2]. For neurons to smoothly and methodically acquire, convey, process, and store information, synaptic structure and function must remain intact. The timely clearance of synaptic contents appears essential for maintaining synaptic function due to the high energy demand and protein turnover ratio in the synapse region [3]. Autophagy has three distinct forms: chaperone-mediated, microautophagy, and macroautophagy (Fig. 1) [4]. Additionally, the contribution of autophagy in synaptogenesis, synaptic elimination, and synaptic transmission has been linked to neurodevelopmental disorders and neurodegenerative disorders. The primary catabolic mechanism that neurons employ to preserve the integrity of synaptic vesicle-dependent transmitter release, organelle quality control, and protein homeostasis of synaptic proteins at postsynaptic locations is macroautophagy [5]. Additionally, there are too many spines, most likely due to poor spine trimming. Neurodegeneration malnutrition is linked to decreased autophagy in the brains of people with Parkinson's or Alzheimer's disease [1,2].

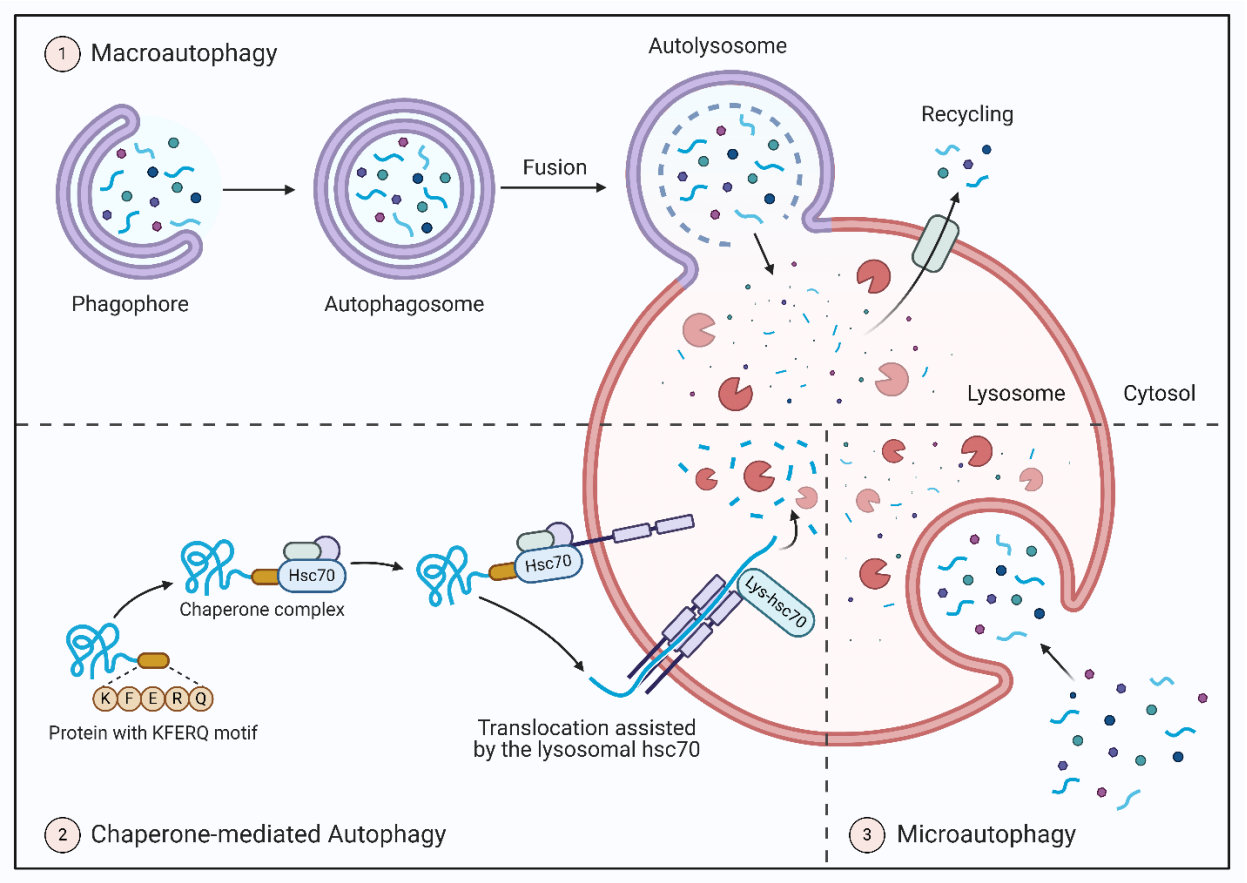


Figure 1. The three main types of autophagy.

Various chemicals and signaling pathways mediate early synaptogenesis, and synaptogenesis is a multi-step process [6]. Two important mechanisms for protein degradation in cells are autophagy and the proteasome-ubiquitin system. Much research has demonstrated the significance of protein degradation

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through the ubiquitin-proteasome system, which is primarily in charge of the turnover of short-lived cytosolic proteins and regulating synaptic growth. This system also degrades damaged organelles and long-lived proteins during synaptic development [7]. The differentiation of mouse neural stem cells has been observed to be accompanied by upregulated autophagy proteins (LC3-II) and higher levels of the synaptic protein synaptotagmin 1 [8,9]. The presence of autophagosomes in the synaptic terminals of cultured hippocampus neurons suggests that autophagy is necessary for synaptogenesis [9]. Furthermore, autophagy-mediated synaptogenesis is facilitated by the mitogen-activated protein kinase signaling pathway. It is important to remember that either increased synaptic production or decreased synaptic deletion might lead to the phenomena of an increased number of synapses. Eliminating unnecessary or superfluous synaptic connections is called synaptic pruning or synaptic elimination. On the other hand, several neurodevelopmental disorders are strongly linked to deficiencies in autophagy that result in inadequate synaptic clearance. A serine/threonine kinase, the mammalian target of rapamycin (mTOR) is essential for cell survival, growth, proliferation, protein synthesis, and autophagy [10]. mTORC1 inhibits autophagy in neurons by localizing presynaptic and postsynaptic locations (or lysosomes) [11]. Rapamycin promotes autophagy in presynaptic terminals, decreases the number of synaptic vesicles (mTOR), which is a serine/threonine, and inhibits the release of evoked dopamine from kinase, which functions as a crucial mediator of cell growth through integrating neurons [12]. Multiple upstream signals provide dopaminergic inputs [13]. At the first stage of autophagosome formation, mTOR prevents autophagy from being activated [14]. Interestingly, mTOR controls local RNA translation at the synapse, suggesting it plays a role in synaptic protein synthesis [15]. New research shows how vital the mTOR transmission signal is for controlling synapses and synaptic plasticity [12,16]. mTOR signaling pathway inhibition Rapamycin increases autophagic activity in mammalian cells and decreases synaptic vesicle densities in presynaptic terminals. A serine/threonine mammalian target of rapamycin inhibits evoked dopamine release from kinase, which functions as a crucial modulator of cell development through integrating neurons [12]. GABA is the primary inhibitory neurotransmitter in the CNS, and autophagy helps postsynaptic terminals break down specific kinds of receptors. Rapid synaptic inhibition in the brain is mediated by GABAA receptors (GABAARs), the main postsynaptic elements of GABAergic synapses. The degradation of a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-type glutamate receptors (AMPARs) in cultivated rat hippocampal neurons upon stimulation is facilitated by glutamatergic N-methyl-D-aspartate receptor (NMDAR)-dependent autophagy, in addition to GABARs, indicating that autophagy plays a role in NMDAR-dependent synaptic remodeling [17]. Previously believed to be only cellular waste disposal units, lysosomes are now recognized as dynamic organelles that play a crucial role in metabolic signaling and nutrition sensing. They facilitate mTORC1 activation by serving as platforms for assessing nutrient availability. Additionally, AMPK and lysosomes interact; for instance, lysosomal damage can activate AMPK through a novel galectin-directed ubiquitin signal transduction mechanism [18]. Axonal endolysosomal trafficking and proper lysosomal activity are essential for neuronal health. Recent discoveries have highlighted the importance of these processes in maintaining the structure and functionality of neurons [19]. Proteinopathic neurodegenerative disorders, which are characterized by the accumulation of misfolded proteins, are often associated with lysosomal failure. Defects in lysosomal breakdown mechanisms can accumulate toxic protein aggregates, which can exacerbate neuronal damage [20]. Autophagy and lysosome-mediated degradation mechanisms are disturbed in a variety of neurological disorders. Understanding how these disrupted pathways might help guide therapeutic strategies to restore cellular homeostasis [21]. Recent research indicates that mRNA trafficking on lysosome-related vesicles is essential for maintaining axonal homeostasis. The fact that neurodegenerative disorders can arise from disruptions in this transport pathway emphasizes the diverse roles that lysosomes play in brain function [22]. The mTOR and AMPK pathways interact intricately on the lysosome to regulate autophagy and cellular metabolism. By phosphorylating components of the mTORC1 pathway, particularly the Regulator complex, AMPK can inhibit mTORC1 and cause mTORC1 to become inactive. This cross-talk ensures that cells adapt to fluctuations in energy levels by appropriately regulating growth and autophagy [23]. Changes in the intensity of synaptic transmission, dubbed synaptic plasticity, are

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assumed to provide a biological equivalent of learning and memory [24-26]. Disrupted synaptic plasticity has been described in mouse models as missing autophagy; nonetheless, much of the mechanism of autophagy affecting synaptic plasticity remains unclear. In certain situations, autophagy controls long-term potentiation [27-30]. Glatigny et al. showed that theta burst stimulation-induced LTP in CA1 is blocked by pharmacologically inhibiting autophagy with Spautin-1 [31]. According to Nikoletopoulou and associates, brain-derived neurotrophic factor (BDNF) inhibits ongoing autophagy in the hippocampus to allow for LTP [32-36]. Since abnormal autophagy has been linked to increased hippocampus mGluR-LTD in a mouse model of fragile X syndrome, autophagy may be involved in long-term depression (LTD) [37]. There are various ways that autophagy could support synaptic plasticity. First, during LTD, autophagy may actively break down AMPA receptors to weaken synapses [17]. Second, other synapse-associated proteins necessary for postsynaptic membrane remodeling during plasticity may be broken down by autophagy [32,37]. Through the breakdown of mitochondria or the endoplasmic reticulum, autophagy may also control the amounts of cytosolic calcium in the pre-or post-synaptic components [38-40]. Additionally, it should be mentioned that several kinases that control autophagic activity, such as mTOR, Akt, and AMPK, are implicated in synaptic plasticity [41-42]. However, it is unclear if these kinases modify synaptic plasticity through autophagy. mTOR comes in two complexes: mTORC1 and mTORC2. In particular, growth hormones, energy levels, and the availability of nutrients all influence mTORC1, a master regulator of cell development and metabolism. mTORC1 is activated on the lysosomal surface, combining signals to prevent autophagy and promote anabolic processes. Dysregulation of the mTOR pathway has been connected to several cancers, underscoring the significance of this system for cell survival and growth [43]. Particularly in neurodegenerative environments, mTORC1 is crucial. Because autophagy is essential for destroying misfolded proteins and damaged organelles, mTORC1 activation can lead to the accumulation of toxic protein aggregates that are suggestive of neurodegenerative diseases [44]. To maintain cellular equilibrium, damaged proteins and organelles are broken down and recycled via a process known as autophagy. In neurons, synaptic autophagy specifically targets synaptic components, including proteins and organelles, to preserve proper synaptic function and plasticity. Dysregulated autophagy has been linked in recent studies to behavioral and synaptic abnormalities linked to psychiatric and neurodegenerative diseases. Damaged synaptic components build up when autophagy is compromised, resulting in synapse loss and dysfunction—two characteristics that are characteristic of neurodegenerative disorders [45]. Dysregulation of this pathway can lead to synaptic dysfunction, which can be seen in conditions like AD, PD, and ALS [46,47]. Autophagy malfunction in AD leads to the buildup of neurotoxic tau proteins and amyloid-beta (Aβ) peptides. Studies have shown that mutations in presenilin-1, a gamma-secretase complex component, impair lysosome function, promote the buildup of Aβ, and result in neuronal death. Additionally, Aβ accumulation and consequent neurodegeneration are caused by defective autophagy in neurons due to decreased Beclin 1 gene expression [3,48,49]. A disruption in autophagic flux is associated with the accumulation of tau tangles and amyloid-beta plaques in Alzheimer's disease, leading to synapse loss and cognitive impairment. In PD, autophagic failure is linked to alpha-synuclein buildup, which results in the death of dopaminergic neurons [50]. One feature of Huntington's disease HD is the rise in mutant huntingtin protein. Impaired autophagy fails to eliminate these protein aggregates, leading to neuronal injury and synaptic dysfunction. Research indicates that HD is characterized by impaired autophagic activity, which speeds up the progression of the illness [21].

2. Therapeutic Opportunities

Early stages of Alzheimer's disease have been linked to impaired synaptic autophagy, which makes it a potential target for therapeutic therapies. Although safety considerations must be taken into account, researchers are investigating ways to modify autophagy to cure various illnesses [51]. As we learn more about synaptic autophagy, new treatments that target this process may be developed to restore synaptic function and stop or halt neurodegenerative disease progression. Pharmacological agents that stimulate autophagy, including rapamycin and resveratrol, have shown promise in preclinical models by improving synaptic function and reducing neurodegeneration [52]. Gene therapy approaches targeting genes

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associated with autophagy are being researched to enhance neuronal survival and restore autophagic flux [53]. Additionally, lifestyle modifications like exercise and calorie restriction may offer non-pharmacological neuroprotection methods because they have been connected to enhanced autophagic activity. These strategies show that various therapy strategies targeting synaptic autophagy can be developed to combat neurodegenerative diseases. To assess their therapeutic potential for reducing AD-related pathology, Bjorkli et al. repurposed two FDA-approved medications, Fasudil and Lonafarnib, which target the synaptic development (i.e., Wnt signaling) and cellular clearance (i.e., autophagic) pathways, respectively. Targeting separate biochemical cascades prevented the progression of AD pathology in 3xTg AD mice. The number of amyloid plaques in dSub, their size and number, CSF Aβ40-42, and p-tau levels decreased with Fasudil treatment. In contrast, lonsafarnib infusions decreased early non-fibrillar forms of tau following overexpression in LEC layer II but did not affect intraneuronal [54]. Both medications affected dense-core amyloid plaques rather than diffuse ones, and the former is linked to microglial activation, neurodegeneration, and cognitive decline in AD patients. Lonafarnib treatment also decreased the number of amyloid plaques but unanticipatedly increased their size [55]. By employing autophagy activator medications, which are thought to be a novel avenue for neuroprotection against misfolded protein toxicity, two structurally related macrolide antibiotics, sirolimus (rapamycin) and tacrolimus (FK506), as well as their derivatives (rapalogues), everolimus and temsirolimus, can pharmacologically block mTORC1 activity, which physiologically occurs during nutrient shortage [56]. These medications are the most potent and effective autophagy activators to date. When rapamycin and tacrolimus bind to the intracellular receptor FK-506-binding protein 12 (FBP12), which identifies a binding site on mTOR, they decrease the kinase activity within mTORC1. The scaffolding property of RAPTOR is counteracted by the complex FBP12-mTOR, which stops mTOR dimerization and activation [57]. It has recently been discovered that rapamycin-dependent mTORC1 inhibition is a potent autophagy activator. In experimental models of neurodegenerative diseases, there is strong evidence that all rapamycin analogs activate autophagy flux, which has neuroprotective effects by preventing the accumulation of aggregation-prone proteins and boosting neuronal viability [58]. The pro-autophagic activity of metformin, the first-line medication for type II diabetes, is mediated by the activation of AMP-activated protein kinase (AMPK), which has been suggested to contribute to its antiproliferative activity. Metformin's long history of use in human therapy has demonstrated excellent tolerability [59]. Through direct LKB1-mediated phosphorylation, metformin induces AMPK activation [60]. Active AMPK either directly activates its downstream effector ULK1 or inhibits mTORC1 to promote the production of autophagosomes [61,62]. Small compounds that disrupt lysosomal activity effectively impede autophagy at its late stage because autophagosomes need to fuse with lysosomes or late endosomes to transport their contents for disintegration. Autophagic substrate buildup, such as misfolded and aggregated proteins and damaged mitochondria, as well as the accumulation of LC3-positive autophagosomes that are unable to fuse and be removed by lysosomes, can be used to visualize this effect [63,64]. Chloroquine (CQ) and its less toxic cousin, hydroxychloroquine (HCQ), are two primary examples of lysosomal lumen alkalizes. Both medications are used to treat infectious disorders like malaria and, more recently, cancer [65]. They are the first and only known autophagy pathway inhibitors authorized for therapeutic use. Depending on dosage and exposure duration, retinopathy and cardiotoxicity have been observed even though short-term CQ/HCQ treatment has been deemed safe [66]. TFEB is a master regulator of lysosomal biogenesis and autophagy. TFEB translocation into the nucleus induced by 15d-PGJ2 requires the production of ROS rather than mTOR inhibition or calcium-dependent calcineurin signaling. TFEB promotes autophagy and lysosome biogenesis upon translocation into the nucleus by upregulating the expression of several genes linked to autophagy and lysosome. At the same time, TFEB transcriptionally increases the expression of ATF4 to encourage apoptosis. The phosphorylation state of TFEB primarily controls its activity. The primary kinase in TFEB phosphorylation is mTORC1 [67,68]. When TFEB is dephosphorylated, it quickly moves into the nucleus to promote lysosome formation and autophagy [69]. Since the nuclear accumulation of TFEB in response to 15d-PGJ2 did not correlate with mTOR phosphorylation status, the translocation of TFEB into the nucleus caused by 15d-PGJ2 is most likely independent of mTOR inhibition. Rab proteins,

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including Rab2 and Arl8, have been identified as potential targets for autophagy enhancement in the nervous system. Activation of these proteins has been shown to increase longevity in neurodegenerative disease models, suggesting their role in promoting autophagy and neuronal health [70]. These strategies show that various therapy strategies targeting synaptic autophagy can be developed to combat neurodegenerative disorders.

3. Conclusion

In conclusion, synaptic autophagy is pivotal in maintaining neuronal health and function, particularly neurodegeneration. This review has highlighted the complex interplay between autophagic processes and synaptic dynamics, underscoring how disruptions in autophagy can contribute to the pathogenesis of neurodegenerative diseases such as AD and PD. As we unravel the mechanisms underpinning synaptic autophagy, it becomes increasingly clear that targeting autophagy-related pathways may offer innovative therapeutic opportunities. Enhancing autophagic function could restore synaptic integrity and improve neuronal communication, ultimately mitigating the progression of neurodegenerative disorders. Future research should focus on discussing the specific molecular targets within the autophagy pathways and developing therapeutic strategies to harness their potential in promoting synaptic resilience and neuronal health. By advancing our understanding of these processes, we can pave the way for novel interventions to preserve cognitive function and improve outcomes for individuals affected by neurodegenerative diseases.

Author Contributions

Mohamed Abd Elsattar Ahmed: writing original draft and reviewing. **Dana Saeed El-Gemaie:** writing original draft and reviewing. **Abdelnaser Hussein Ahmed Hussein:** writing original draft. **Al-Hassan Soliman Wadan:** Conceptualization, editing, writing original draft and reviewing.

Conflict of interest

The authors declare no conflict of interest.

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