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·Review·

Molecular network of neuronal autophagy in the pathophysiology and treatment of depression

Jack Jia[1,2], Weidong Le[3]

[1]*Sbarro Institute for Cancer Research and Molecular Medicine, Center of Biotechnology, College of Science and Technology, Temple University, Philadelphia, PA, USA*

[2]*New Jersey Medical Institute, Trenton, NJ, USA*

[3]*Center for Translational Research on Neurological Disease, First Affiliated Hospital, Dalian Medical University, Dalian 116011, China*

Corresponding author: Weidong Le. E-mail: wdle@sibs.ac.cn

Major depressive disorder (MDD) is a complicated multifactorial induced disease, characterized by depressed mood, anhedonia, fatigue, and altered cognitive function. Recently, many studies have shown that antidepressants regulate autophagy. In fact, autophagy, a conserved lysosomal degradation pathway, is essential for the central nervous system. Dysregulation of autophagic pathways, such as the mammalian target of rapamycin (mTOR) signaling pathway and the beclin pathway, has been studied in neurodegenerative diseases. However, autophagy in MDD has not been fully studied. Here, we discuss whether the dysregulation of autophagy contributes to the pathophysiology and treatment of MDD and summarize the current evidence that shows the involvement of autophagy in MDD.

Keywords: major depressive disorder; autophagy; mTOR; antidepressant

Introduction

Major depressive disorder (MDD) is a prevalent, heterogeneous illness characterized by depressed mood, anhedonia, low energy or fatigue, and altered cognitive function. Other symptoms, such as sleep and psychomotor disturbances, feelings of guilt, low self-esteem, suicidal tendencies, as well as autonomic and gastrointestinal disturbances, are also often present[1, 2]. If left untreated, it can be fatal. The lifetime prevalence of MDD is ~17% of the population and results in tremendous secondary costs to society[3, 4]. The 'gold standard' for depression treatment involves a combination of psychotherapy and medication. Unfortunately, current anti-depressant medications do not help everyone, and both normally take a number of weeks of regular treatment before they begin to have an effect[5]. Diagnosis of MDD is based on relatively subjective assessments of diverse symptoms representing multiple endo-phenotypes[6]. And most current treatments are based on monoamine neurochemical alterations in MDD[7]. Therefore, knowledge of the mechanism of MDD will help the development of effective treatment. As currently known, MDD is a complicated multifactorial induced disease associated with both genetic and environmental factors, and the detailed molecular mechanisms underlying the pathogenesis remain difficult to elucidate. The pathophysiology of MDD involves complex signaling networks[8], including alterations of cytokines, monoamine-deficiency in the central nervous system, and dysfunction of the glutamate system. Moreover, MDD is most often related to disturbed neurogenesis, structural and functional alterations of several limbic and cortical regions[9]. It is also proposed that dysfunction of synaptic plasticity is a basis of the etiology of MDD[10, 11]. Furthermore, postmortem brain tissues from MDD patients also display increased apoptotic stress and apoptosis-related factors[12, 13]. Recent studies

indicate that neuronal autophagic signaling pathways are also involved in MDD.

Autophagy is important for most cells in various tissues including the central nervous system; it is sensitive to the accumulation of toxic proteins/damaged organelles[14]. Therefore, alteration of autophagy during neurodevelopment and synaptic plasticity might cause abnormal development and synaptic malfunction. In addition, impairment of autophagy pathways may lead to the accumulation of pathogenic proteins and damaged organelles, which may finally result in neurological disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD)[15, 16]. Recently, many antidepressants were found to be involved in the neuronal autophagy signaling pathway. The co-chaperone FKBP5/FKBP51 (FK506 binding protein 5) acting as an antidepressant plays a role in autophagy[17]. These findings suggest that neuronal autophagy signaling pathways play an important role in MDD, so this review focuses on neuronal autophagy that is involved in MDD and is affected by antidepressants.

Neuronal Autophagy Dysregulation in Neurodegenerative Diseases

Basal Autophagy May Be Beneficial and Required for Normal Function of Neurons

Autophagy is extremely important in maintaining cellular homeostasis, which requires the continuous turnover of nonfunctional proteins and organelles[18]. Neurons are highly postmitotic, with specialized structures for intercellular communication. Therefore, neuronal integrity is more sensitive to alterations in basal autophagy than that of non-neurons[14]. Recent findings show that autophagy in neurons is indeed constitutively active, and that autophagosomes accumulate rapidly when their clearance is blocked[19, 20].

Many studies have shown that autophagy protects neurons under stress conditions. Jeong *et al.* showed that sirtuin 1 (SIRT1) overexpression prevents prion peptide neurotoxicity by inducing autophagy, while preventing autophagy by knock-down of autophagy-related 5 (Atg5) abolishes SIRT1-induced neuroprotection[21]. Shen *et al.* discovered that neuroautophagy positively regulates synaptic development, and overexpression of Atg1, a key regulator of autophagy, is sufficient to induce high levels of autophagy and subsequent enhancement of synaptic growth. In contrast, reducing autophagy results in the reduction of synapse size[22]. Moreover, the autophagosomal marker LC3-II and Akt and mammalian target of rapamycin (mTOR) dephosphorylation have a time-course coincident with degradation of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor GluR1 in neurons, which indicates that autophagy is a positive regulator of N-methyl-D-aspartate receptor (NMDAR)-dependent synaptic plasticity[23]. Neuronal autophagy may play important roles in the structural refinement of neurite growth, neuronal differentiation, synaptic growth, or synaptic plasticity, which ensures the formation of appropriate neuronal connections and their functions[24, 25].

Aberrant Autophagy Leads to Neurodegenerative Diseases, Including Depression

Dysregulation of autophagy might cause a cellular traffic-jam during neuronal development and synaptic plasticity, leading to neurodevelopmental disorders; it also might lead to the accumulation of misfolded protein aggregates and damaged organelles, leading to neuronal dysfunction and even death. Disruption of autophagy after spinal cord injury may contribute to endoplasmic reticulum-stress-induced neuronal apoptosis[26]. Neuron-specific knockout of the key autophagic gene Atg5 or Atg7 leads to accumulation of intracellular protein aggregates and neuronal death[19, 20].

Autophagy-lysosome defects occur early in the pathogenesis of AD and have been proposed to be a significant contributor to the disease process[27]. Nixon *et al.* provided evidence from electron microscopy that autophagy is extensively involved in the neurodegenerative process in AD[28]. And the transport of autophagic vacuoles and their maturation to lysosomes might be impaired in AD[29].

Autophagy of mitochondria can be regulated by parkin, PINK1 and DJ-1, and importantly, mutations in these proteins are thought to cause familial PD[30]. Xilouri *et al.* showed that α-synuclein, a major constituent of Lewy bodies, is degraded by autophagy in PD[31]. And recently, researchers have established an essential link between mitochondrial autophagy impairment and dopamine neuron degeneration in an *in vivo* model based on genetic deletion of either parkin or PINK1 (known PD genes)[32].

An autophagy defect has also been suggested by genetic studies of amyotrophic lateral sclerosis (ALS) and frontotemporal lobe dementia (FTD). For instance, mutations in UBQLN2 and SQSTM1/p62 have been reported in ALS and FTD[33-35]. In fact, UBQLNs are present in autophagosomes and bind LC3 in a complex while SQSTM1/p62 binds ubiquitinated proteins and LC3[36, 37]. Besides, evidence of direct alteration of the autophagic pathway, bypassing mTOR modulation has been shown in epileptogenesis[38]. As for depression, increased autophagosomal marker LC3-II has been reported in a cellular model of chemically-induced long-term depression (LTD)[18].

Interestingly, in the parkinsonian mimetic 6-hydroxydopamine (6-OHDA) model, the 6-OHDA-induced apoptosis is prevented by treatment with the early-phase inhibitor of autophagy, 3-methyladenine, but the late-phase inhibitor of autophagy, bafilomycin A1, aggravates this apoptosis[39]. In fact, most evidence points to autophagy as a protective process in neurons, but other studies also provide genetic and cellular evidence that otherwise argues for a role of autophagy in promoting neuronal death[40]. Autophagy might show a Janus face, too much or not enough would lead to disorders like neurodegenerative diseases[41].

Autophagy-Related Pathways in Depression

Dysregulation of the autophagic pathway in neurons may result in depression[42]. Autophagy is regulated by intracellular and extracellular signals *via* at least three pathways: (1) The mTOR-dependent pathway: the Atg1/unc-51-like kinase complex acts downstream of mTOR complex 1 (mTORC1); (2) the PI3K/beclin1 pathway; and (3) the Ca^{2+} pathway[43]. mTORC1 integrates nutrients, energy, growth factors, and amino-acid signaling; once activated, mTORC1 inhibits autophagy by acting on the Atg1 kinase complex, while the beclin complex positively regulates autophagy[44, 45]. It is now well established that Ca^{2+} is a regulator of autophagy, while it is still unclear whether Ca^{2+} is a positive or a negative regulator[46].

The PI3K-Akt-mTOR pathway is related to depression[47]. Decreased AKT1/mTOR mRNA expression has been reported in short-term bipolar disorder[48]. A recent study showed that neuronal stimulation induces NMDAR-dependent autophagy through the PI3K-Akt-mTOR pathway in a cellular model of LTD[25]. Simultaneously, metabotropic glutamate receptor (mGluR) activation results in increased PI3K-mTOR signaling and activation of protein synthesis near synapses in a mouse model of LTD[25]. And inhibition of protein synthesis or mTOR signaling blocks mGluR-dependent LTD[49]. In fact, mTOR signaling lies at the crossroads of multiple signals involved in protein synthesis and impairment of autophagy during neurodegeneration[50, 51]. Activation of mTOR has been functionally linked with local protein synthesis in synapses, resulting in the production of proteins required for the formation, maturation, and function of new spine synapses[50]. In the meantime, mTORC1 inhibits autophagy, an essential protein-degradation and recycling system[52]; for example, PI3K-Akt-mTOR is associated with autophagy impairment and is impaired in mild cognitive impairment and AD[53]. mTOR regulates both neuroprotective (*via* autophagy) and neuroregenerative (*via* protein synthesis) functions in various diseases of the central nervous system[42].

Brain-derived neurotrophic factor (BDNF) plays an essential role in neuronal plasticity, and downregulation of its expression/function is reproduced in a variety of animal models of MDD[54]. Indeed, the neuroprotective effect of BDNF not only prevents apoptosis by inhibiting caspase activation but also promotes neuron survival through modulation of autophagy[55]. And BDNF can be mediated by autophagy through the PI3K-Akt-mTOR pathway[56]. These results also suggest that autophagy plays an important role in MDD.

In addition, Cummings *et al.* showed that the minimal requirements for inducing LTD involve simply a transient influx of Ca^{2+} into the postsynaptic cell *via* either NMDARs or voltage-dependent Ca^{2+} channels[57].

We assume that cellular stress in the form of reactive oxygen species or other factors causes proteins to misfold and aggregate. Under normal conditions, this would in turn diminish or overwhelm degradation *via* the autophagy or ubiquitin–proteasome system. However, with autophagy impairment, cells would be unable to clear aggregates and damaged organelles. And additional mitochondrial dysfunction, excitotoxicity, and pore formation lead to increased intracellular Ca^{2+} levels, ultimately resulting in necrosis and apoptosis[58]. But excessive autophagy also induces apoptosis[59]. In fact, injury and apoptosis of

hippocampal tissue is the reason for MDD[60]. From this point of view, autophagy would be an accomplice of MDD (Fig. 1).

Antidepressants and Autophagy

Beyond their impact on monoaminergic neurotransmission, recent reports have evidenced that many antidepressants affect autophagy pathways in the process of anti-depression[17, 61]. Several studies have demonstrated that cellular autophagy markers are upregulated upon treatment with antidepressants[62]. Many antidepressants like sertraline activate mTOR. However, antidepressant activity of rapamycin (an mTOR inhibitor) has also been reported in an animal model[63]. Moreover, autophagic markers, such as beclin1, are increased following antidepressant treatment in mouse brain[64]. Autophagy might be a double-edged sword in MDD, which may be the reason why some MDD patients remain resistant to certain antidepressant medications.

Antidepressants Affect the Autophagic Pathway

The antidepressant drug amitriptyline (AMI) and the selective serotonin re-uptake inhibitor citalopram (CIT) have been reported to increase the expression of the autophagic markers LC3-II and beclin1, but venlafaxine fails to exert these effects[65]. AMI- and CIT-induced autophagy is functional in terms of autophagic flux, and is partially mediated by class III PI3K- and ROS-dependent pathways[62]. FKBP51 can synergize with antidepressants by binding beclin1, changing its phosphorylation and enhancing markers of autophagy and autophagic flux as well as triggering autophagic pathways[17]. Chronic paroxetine treatment of a depression-relevant stress model revealed that the physiological effects of antidepressants on behavior and autophagic markers depend on FKBP51[64]. Trehalose may have antidepressant-like properties through its enhancement of autophagy[66]. Lithium, which has been used for several decades to treat manic-depressive illness (bipolar affective disorder), induces autophagy, thereby promoting the clearance of mutant huntingtin and alpha-synucleins from experimental systems[67]. Thus some but not all antidepressants affect autophagy.

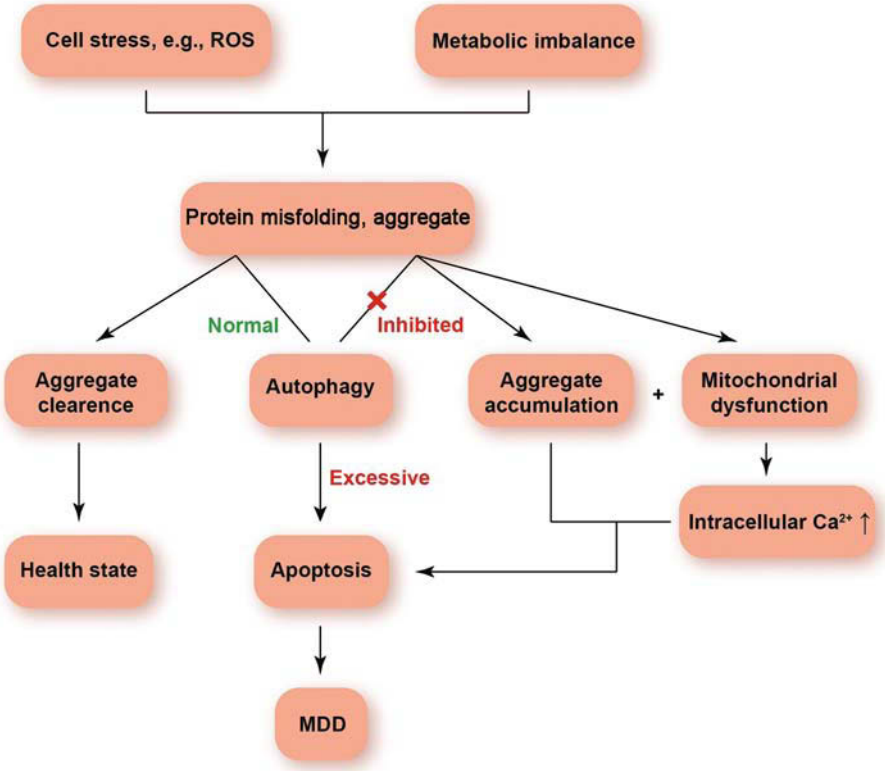

Fig. 1. Possible involvement of autophagy in the pathogenesis of MDD.

Autophagy Is a Potential Mechanism of Antidepressant Action

Antidepressants are commonly used in the treatment of cancer patients with depression, and the underlying mechanisms are also related to inducing autophagy. Elevated levels of the autophagic protein beclin-1 and the cellular redistribution of the marker LC3 have been found in C6 glioma cells treated with the antidepressant desipramine (DMI), which induces autophagic cell death by the formation of autophagosomes[61]. Moreover, activation of the PI3K-AKT-mTOR pathway, which is considered to be a negative regulator of autophagy, is also inhibited by DMI. Furthermore, DMI activates PERK-eIF2α and ATF6 of the endoplasmic reticulum stress pathway to induce autophagy in C6 glioma cells[61]. As another example, the tricyclic antidepressant imipramine stimulates the progression of autophagy, and exerts antitumor effects on PTEN-null U-87MG human glioma cells by inhibiting PI3K-Akt-mTOR signaling and by inducing autophagic cell death[68]. The antidepressants maprotiline and fluoxetine, which are novel pro-autophagic agents, induce autophagic programmed cell death (PCD) in the chemoresistant Burkitt's lymphoma (BL) cell line DG-75; this does not involve caspases, DNA fragmentation, or PARP cleavage, but is associated with the development of cytoplasmic vacuoles, all consistent with an autophagic mode of PCD[69]. Therefore, autophagy-initiating mechanisms should be considered as a pharmacological target to improve the treatment of depression.

Antidepressants and the mTOR-Dependent Signaling Pathway

The classic antidepressant drugs inhibit the PI3K-Akt-mTOR signaling pathway[68]. Fluoxetine, an antidepressant that inhibits the reuptake of serotonin in the central nervous system, promotes neurogenesis and improves the survival rate of neurons. A further study suggested that the improvement of neuron survival is achieved by upregulated expression of the phosphorylated AKT protein, which is a key factor in the PI3K-Akt-mTOR signaling pathway[70]. Another study showed novel *in vitro* evidence that some antidepressant drugs promote dendritic outgrowth and increase synaptic protein levels through mTOR signaling[71]. Warren *et al.* demonstrated that administration of fluoxetine in combination with methylphenidate induces mTOR activity in rats[72]. A rapid antidepressant and nonselective NMDAR antagonist, ketamine, activates the mTOR signaling pathway, leading to increased synaptic proteins in the rat prefrontal cortex[73].

In fact, most previous reports focused on the mTOR synaptogenesis by antidepressants[74]. Probably, neuronal autophagy-related mTOR signaling pathways could also explain the mechanism of antidepressant function, for mTOR signaling is at the crossroads between protein synthesis and impairment of autophagy in neurodegeneration[50, 51]. However, more studies are definitely needed.

Antidepressants and the mTOR-Independent Pathway

Besides, some antidepressant drugs seem to act *via* an mTOR-independent pathway to affect autophagy. For example, autophagy triggered by AMI and CIT is partially mediated by beclin pathways since 3-methyladenine slightly diminishes the effects of AMI. The antidepressant maprotiline has been shown to inhibit dendritic γ-amino-butyric acid- and NMDA-induced increases in Ca^{2+} in primary cultured rat cortical neurons[75] and in human prostate cancer cells[76]. Further, calcium channel blockade affects the processes related to antidepressant-induced changes in the crosstalk between α1- and β-adrenergic receptors[77]. In fact, it is now well established that intracellular Ca^{2+} is one of the regulators of autophagy[46]. All these results showed that many antidepressants are involved in autophagy *via* diverse pathways to synergize with antidepressant action. However, more detailed studies are needed to characterize the autophagic pathways in depression and their participation in antidepressant mechanisms[42].

Conclusion

In summary, MDD is one of the most prevalent debilitating public health problems worldwide. The current review summarized and discussed the possible involvement of neuronal autophagy in MDD. Although the molecular mechanisms underlying MDD are still largely unclear, we proposed that neuronal autophagy signaling network is also implicated in the pathogenesis of MDD and the mechanisms of some antidepressant actions. Further understanding of neuronal autophagy regulation in MDD is expected to contribute to the development of therapeutic interventions in MDD.

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