frontiers in Psychiatry

MINI REVIEW
published: 15 May 2019
doi: 10.3389/fpsyt.2019.00337

Is There a Role of Autophagy in Depression and Antidepressant Action?

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Autophagy has been recognized as evolutionary conserved intracellular pathway that ensures energy, organelle, and protein homeostasis through lysosomal degradation of damaged macromolecules and organelles. It is activated under various stress situations, e.g., food deprivation or proteotoxic conditions. Autophagy has been linked to several diseases, more recently also including stress-related diseases such as depression. A growing number of publications report on the role of autophagy in neurons, also referred to as "neuronal autophagy" on the one hand, and several studies describe effects of antidepressants—or of compounds that exert antidepressant-like actions—on autophagy on the other hand. This minireview highlights the emerging evidence for the involvement of autophagy in the pathology and treatment of depression and discusses current limitations as well as potential avenues for future research.

Keywords: autophagy, depression, antidepressant, stress, FKBP51 signalling

OPEN ACCESS

Edited by:
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Specialty section:
This article was submitted to Molecular Psychiatry, a section of the journal Frontiers in Psychiatry

Received: *14 September 2018*
Accepted: *29 April 2019*
Published: *15 May 2019*

Citation:
Gassen NC and Rein T (2019) Is There a Role of Autophagy in Depression and Antidepressant Action? Front. Psychiatry 10:337. doi: 10.3389/fpsyt.2019.00337

DEPRESSION IS A PREVALENT AND SEVERE DISEASE

Worldwide, depression is one of the most frequent clinical conditions and the leading cause of disability affecting more than 300 million people of all ages, according to World Health Organization (WHO) statistics (http://www.who.int/news-room/fact-sheets/detail/depression). Depression is characterized by a cluster of symptoms that include depressed mood, fear, feelings of worthlessness, loss of energy and interest, reduced responsiveness to pleasurable stimuli, lack of appetite, cognitive impairment, and sleep disturbances (1). A high percentage of seriously depressed patients receive no appropriate treatment, even in developed countries (2). Suicidal ideation is a further characteristic of depression and up to 15% of severely depressed individuals commit suicide. Depression represents also a major independent risk factor for other diseases like cardiovascular disease, dementia, diabetes, and osteoporosis (3, 4).

The high complexity of this mental disorder accounts for the difficulties in elucidating its molecular underpinnings. Overall, it has been increasingly accepted that a multitude of factors ranging from genetic predisposition to environmental challenges contribute to the pathophysiology of depression. In addition to the analysis of specific targets, research efforts increasingly resort to screening platforms to probe the genome, epigenome, etc. in an unbiased way. Examples of the major specific systems under investigation are monoaminergic, glutamatergic, and stress hormone systems, neuropeptides as modulators of the neuronal cell function including neurogenesis, neuronal morphology, and intracellular signaling pathways.

In genetics, huge efforts produced intriguing results; however, the field is haunted by the lack of consistency and reproducibility [for a recent review, see Ref. (5)]. Thus, increasingly large cohorts are investigated, and meta-analyses are employed to probe several hundred thousands of individuals (6).

Nevertheless, not the least due to the difficulties to move from gene association to molecular mechanism, hypothesis-driven approaches continue to be pursued intensely.

Monoamine deficiency was the first hypothesis unfolded over several years, tracing back more than half a century, and probably is the most influential one (7, 8). It postulates lack of monoaminergic neurotransmitters and thus impaired synaptic neurotransmission as cause for depression; several newer antidepressant drugs were developed based on this hypothesis. Other examples include glutamatergic dysfunction and the corticosteroid hypothesis of depression (7, 9). A vast array of studies supports the link between the stress hormone system and depression (9, 10). More specifically, impaired corticosteroid receptor function has been suggested to result in inappropriately high secretions of corticotropin releasing hormone (CRH), vasopressin, adrenocorticotropin, and cortisol (9). A role of autophagy in depression is a more recent hypothesis put forward (11), which can be viewed as one of the ramifications of the stress response as outlined below.

AUTOPHAGY IS A CELLULAR HOMEOSTASIS PROCESS AND PART OF THE STRESS RESPONSE

Autophagy is a pivotal process to ensure homeostasis of cells, and thus of tissues and the organism, in physiological as well as pathological situations (12, 13). This highly conserved mechanism leads to the degradation of damaged cytosolic proteins, aggregates, organelles, and also pathogens through a step-wise process. The basic mechanism is detailed in several excellent reviews (13–15), so it is described here only briefly: Autophagy involves a series of autophagy-related genes (ATGs), originally identified in yeast. Initially, membrane material is excised, most likely from the endoplasmic reticulum, giving rise to a membrane sac that is further expanded to form a double membrane vesicle called autophagosome. To be degraded material is enclosed into this vesicle; selected additional material can be transferred into the autophagosome. Degradation is achieved upon fusion with lysosomes to form autolysosomes: From the initial isolation of membrane material needed for the formation of autophagosomes to the final fusion step, autophagy involves a number of proteins governing membrane dynamics (16). There are different types of autophagy, with macroautophagy being the most commonly described one (15); this review only deals with macroautophagy, because research on the emerging subject of neuronal autophagy did not yet aim at specifying the type of autophagy.

The crucial physiological role of autophagy is reflected in its links to several diseases and the increasing efforts to exploit this process for pharmacological intervention (17–21). Initially, autophagy was identified as response to calorie restriction to maintain energy homeostasis (22). Today, several pharmacological and environmental factors are known to induce autophagy, in particular various kinds of stressors (13, 17). Thus, autophagy is an important facet of the stress response, and like the stress response in general, autophagy is a beneficial process, but excess activation can be detrimental under certain conditions (23, 24). For example, apoptosis (often referred to as Type I cell death) and autophagy are considered mutually exclusive (13). Others debate this exclusiveness and argue that excessive autophagy can cause type II cell death characterized by the formation of large autophagic vacuoles (25, 26).

Chronic stress in mice, which frequently is used to model depression (27, 28), also has been reported to enhance autophagy [for recent examples, see Refs. (29, 30)]. The observation that a further increase in autophagic markers goes along with the reversal of the behavioral effects again argues in favor of autophagy being a beneficial component of the stress response in general (13, 30). Nevertheless, evidence also has been provided for a role of autophagy induction for depressive-like behavior and cognitive impairment induced by prenatal stress (31). Very recently, inhibition of autophagy was shown to attenuate the induction of depressive-like behavior by ecstasy in rats (32).

AUTOPHAGY IN DEPRESSION: EVIDENCE FROM DISEASE AND DISEASE MODEL STUDIES

In human, a study using a small sample size found elevated expression of autophagy genes in blood mononuclear cells from individuals suffering from major depression in comparison to healthy controls (33). Similarly, decreased mRNA expression of AKT1 and mTOR was found in individuals with short-term bipolar disorder compared to healthy controls (34), which might lead to the induction of autophagy. Similarly, a post-mortem study revealed compromised mTOR signaling in the prefrontal cortex in major depressive disorder (35). How could this be reconciled with the observation that enhanced autophagy response in blood mononuclear cells to *ex vivo* antidepressant treatment predicts clinical treatment success (36)? Similar to the stress response in general, autophagy is a beneficial response up to a certain limit, so we hypothesize that this adaptation might be insufficient in some (disease) cases and needs further boosting through various kinds of treatments.

Short-term calorie restriction, one of the most efficient inducers of autophagy (22), has been reported to have antidepressant effects in human and antidepressant-like effects in mice, while the effects of long-term calorie restriction are controversial (37). Likewise, physical exercise has been shown both to enhance autophagy (38) and to reduce depressive symptoms in human (39). Nevertheless, given the plethora of effects of both calorie restriction and exercise, these studies only provide a rather vague support of a potential link between autophagy and depression.

Studies more directly documenting a link of autophagy to psychiatric disease mainly were performed with animal models, with all the debated limitations that come with animal models that try to replicate aspects of depression (27). Maternal separation (40) increased autophagic markers in the prefrontal cortex, but not in the hippocampus (41). This is mimicked by the differential effect of corticosterone in primary astrocytes from these brain regions (42), while another study found that prenatal stress significantly elevated autophagy markers in the hippocampus of male offspring (31). On the other hand, signs of decreased

autophagy also have been reported in depression-relevant animal models. For example, chronic unpredictable stress decreased autophagic markers (43, 44). LPS as well as unpredictable chronic mild stress induced depression-like symptoms in rodents along with reduced expression of autophagic markers (45, 46). Furthermore, inhibition of the autophagy initiator Beclin1 (47) induced depression-like behavioral changes in mice (48). Thus, no consistent picture of enhanced or reduced autophagy in depression yet emerges from animal models. Further, it is difficult to conclude about functional autophagy, as flux assays or determining turnover of long-lived proteins is complicated to perform in mice.

AUTOPHAGY IN DEPRESSION: EVIDENCE FROM TREATMENT EFFECTS

Given the scarcity of studies on disease correlation, the hypothesis that autophagy is involved in depression mainly is based on the effects of antidepressants on autophagy. One of the earliest hints for a role of antidepressants in autophagy was the observation of autophagy-associated structures in the cytoplasm upon treatment of cells with the tricyclic antidepressant clomipramine (chlorimipramine) (49). This phenomenon could be caused by either induction of autophagy or blocking the autophagy flux, thus actually blocking functional autophagy. It should be noted here that the conclusion of active autophagy often is based on the mere appearance of autophagic markers, which is not correct in the absence of experiments assessing the autophagic flux or turnover of long-lived proteins (50). Employing appropriate experiments, it was shown later that desmethylclomipramine, the active metabolite of clomipramine, interferes with the autophagic flux and thus functional autophagy (51). In contrast to the effect of clomipramine, another tricyclic antidepressant, amitriptyline, was found to increase autophagy in primary neurons and astrocytes, similarly to the selective serotonin reuptake inhibitor citalopram; however, the selective serotonin and noradrenaline reuptake inhibitor venlafaxine did not alter autophagy (52, 53). Thus, it appears that antidepressants diversely impact functional autophagy, possibly also in a cell-type-dependent manner.

Conspicuously, the canonical autophagy inducer rapamycin has been found to exert antidepressant-like effects (54, 55), emphasizing the role of the mTOR pathway (56). Conversely, several other established antidepressants and compounds that are reported to exert antidepressant-like effects were shown to modulate autophagy in various experimental models. Among the established antidepressants are the tricyclic antidepressants desipramine, nortriptyline, and imipramine, the tetracyclic antidepressants maprotiline and mianserin, the noradrenergic and serotonergic antidepressant mirtazapine, the selective serotonin reuptake inhibitors fluoxetine (Prozac), sertraline, and paroxetine, the serotonin-norepinephrine reuptake inhibitor desvenlafaxine, the atypical antidepressant agomelatine, lithium [for a review, see Ref. (57)], and the anticonvulsant valproic acid. Further drugs with both antidepressant-like effects and impact on autophagy include trehalose, hypericin, which is one of the principal components of Saint John's wort, Salvianolic acid B, rosiglitazone, silibinin, dapsone, geldanamycin, α-tocopherol, and extracts of Euryale ferox Salisb (see **Table 1** for more details and citations). Of note, also electroconvulsive therapy, which particularly is used for severe or treatment-resistant depression (58), was reported to enhance autophagy (59).

Mechanistically, antidepressants appear to address various pathways to impact autophagy. For example, FKBP51, which is a glucocorticoid receptor and stress regulator linked to psychiatric diseases (84–86), has been shown to be required for the effects of antidepressants on both autophagy and depressive-like behavior (36, 87). Another very recent study discovered that the previously reported effects of antidepressants on the acid sphingomyelinase (ASM) (88, 89) trigger a pathway leading to upregulation of autophagy, which is required for the behavioral effects in mice (48). More specifically, this pathway involves the accumulation of antidepressants in lysosomes, where they inhibit ASM. This leads to an increase in sphingomyelin and finally of ceramide in the endoplasmic reticulum. Ceramide, in turn, activates the phosphatase PP2A, which stimulates the kinase ULK, a known activator of autophagy (48).

Of the pleiotropic effects of the mood stabilizer lithium (90), its autophagy-inducing action does not operate through GSK3β, but by inhibition of inositol monophosphatase (91). Despite first glimpses, overall there is considerable lack of mechanistic understanding of how antidepressants link to autophagy. This is partly due to the incomplete knowledge about the molecular interaction partners of antidepressants. Progress in this direction (92) will help elucidating the molecular connection to autophagy. This may also contribute to sorting the actions of antidepressants, because not everything antidepressants do has to be related to depression treatment. Another long-standing conundrum in understanding how antidepressants work is the observation that clinical effects typically take weeks to become manifest, while known targets like neurotransmitter transporters are affected immediately. It is unlikely that autophagy will offer an obvious solution. Arguably, it contributes to starting a process of neuronal reorganization that ultimately constitutes the transition from disease to health (cf. **Figure 1**). Neurogenesis might be part of this process, as extensively discussed elsewhere (93). In this context, it is intriguing that autophagy increases adult neurogenesis (94, 95); thus, it is possible that antidepressants and lithium operate, at least in part, through autophagy to induce neurogenesis (90, 96).

The vast majority of publications report an increase in autophagy by antidepressants. This is also the case for the fast-acting antidepressant ketamine (75), even though it is known to enhance mTOR activity (98). However, as alluded to above, flux assays are missing in many studies (cf. **Table 1**), which may lead to erroneous interpretation and conflicting results. More specifically, many of these reports merely observed an upregulation of autophagic markers, for example, lipidation of LC3B (i.e., an increase in the ratio of LC3II/I), which is not sufficient to make conclusions about functional autophagy. Overall it appears more likely that antidepressants diversely affect autophagy. Another important issue is the concentration at which antidepressants are administered in experimental models. This concentration typically is in the range of 10 μM n cell culture or 10 mg/kg in

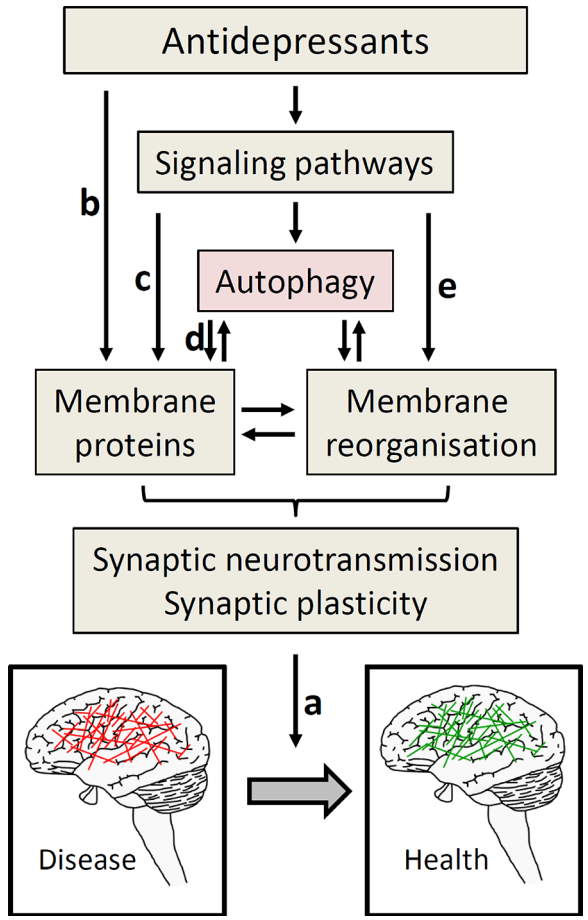

FIGURE 1 | Autophagy as part of antidepressant action. To move from diseased (depressed) to healthy state, ultimately a change in neuronal activity is required (A). To achieve this, several ways of antidepressant actions are proposed including effects on hormonal systems, immune system, and neurogenesis, which all might be intertwined with autophagy (97); this figure focuses on synaptic neurotransmission. The by far most often described effect of antidepressants on synaptic neurotransmission operates through directly blocking neurotransmitter reuptake transporters (part of the membrane proteins, (B). These transporters may also be addressed through signaling pathways that regulate their expression and/or function (C), not part of this review). The role of autophagy in antidepressant action frequently is explained by maintaining protein homeostasis in general, and the functional integrity of membrane proteins involved in synaptic neurotransmission in particular (D). These membrane proteins comprise not only transport proteins, but also, e.g., presynaptic SNARE proteins engaged in neurotransmission. Given the similarity of membrane dynamic processes in autophagy and synaptic neurotransmission, and to reconcile the diverse findings of antidepressant effects on autophagy, we also discussed the hypothesis that antidepressants address pathways that change membrane organization, directly linking to synaptic neurotransmission (E).

animal experiments, sometimes even higher. While it has been reported that similar doses can be reached in the brain (99, 100), effects reached at concentrations based on the results of therapeutic drug monitoring (101) may more closely mimic the clinical situation. For example, paroxetine (used at the therapeutic drug dose of 120 ng/ml = 0.9 μM) and amitriptyline (used at the therapeutic drug dose of 120 mg/ml = 0.37 μM) enhanced the expression of autophagy markers in blood mononuclear cells from depressed patients exposed to these reduced concentrations *ex vivo* (36).

CONCLUSION AND OUTLOOK

Over the last few years, several studies provided evidence for a link of autophagy to the pathophysiology and treatment of depression. Despite impressive progress, the mechanism is far from being understood. This is not surprising for a complex disease like depression, which poses particular experimental challenges and epistemological limitations, as exemplified by the complex mechanisms linking stress with depressive behavior. The molecular effects of antidepressants ultimately need to produce alterations in the pattern of neuronal activity that underlie the transition between diseased and healthy status (**Figure 1**). This means that some neuronal activity needs to be decreased and some needs to be increased. Interestingly, neuronal stimulation not only induces autophagy (102); increased autophagy also impacts synaptic function. For example, induction of autophagy by mTOR inhibition in presynaptic terminals rapidly alters presynaptic structure and reduces neurotransmission (103). Conversely, loss of autophagy slows down synaptic neurotransmission while gain of autophagy increases it (104). The latter finding has been conceptualized by the function of autophagy in protein homeostasis by removing damaged proteins, in this case those involved in synaptic vesicle exocytosis in particular (104, 105). Intriguingly in a mouse model of learnt helplessness evoking depressive-like behavior, decreased levels of the presynaptic vesicle membrane docking and fusion SNARE protein Snap25a occur along with impaired autophagy; administration of fluoxetine attenuates both these effects (106). The SNARE proteins are important components of the membrane reorganizing machinery at the synaptic membrane, and there is an interdependence between autophagy and synaptic vesicle trafficking (107, 108). In addition, electroconvulsive therapy enhances not only autophagic markers (59) but also the membrane trafficking machinery (109).

In light of the presumably diverse impact of antidepressants on autophagy, enhanced recycling of distinct synaptic proteins by inducing autophagy is unlikely to fully picture the mechanism of antidepressants. Given the fact that autophagy needs the activity of a number of membrane reorganizing and membrane trafficking proteins, we consider it plausible that processes impacting autophagy may also impact membrane reorganizing processes at the synapse, and thus would not require the later steps autophagy (cf. **Figure 1**). In general, these processes could be fast, because they do not necessarily require the synthesis of new proteins. They could limit synaptic neurotransmission when autophagy and neurotransmission compete for additional membrane material; conversely, autophagy would promote neurotransmission if there are shared mechanisms for the generation and fusion of membrane material. Thus, it will be of great interest to learn about the conditions under which autophagy increases or decreases synaptic neurotransmission, possibly in a neurotransmitter-specific fashion.

TABLE 1 | Overview of the various autophagy-impacting compounds that are used as antidepressants or reported to exert antidepressant-like effects in animal models.

Compound/ Antidepressant	Experimental system	Results, autophagic markers	Flux, LLP	Citation
Clomipramine*,	Human glioma cells	Autophagy-associated structures	no	(49)
Desmethyl-clomipramine	HeLa Cells, ATG5$^{-/-}$MEFs	LC3BII/I up, increase in DM structures, flux blocked, LLP degradation down	yes	(51)
Amitriptyline*	Primary rat astrocytes and neurons, ATG5$^{-/-}$MEFs	Increased autophagy (LC3BII/I, Beclin1 up)	yes	(52)
	Mouse stress model, patient blood cells, HEK cells, rat cortical astrocytes	ATG12, LC3II/I, Beclin1, pAkt1 and VPS34 were up, increased flux	yes	(36)
	Corticosterone-stressed mice	Increased autolysosomes, affects pBeclin, pULK, increased p62	no	(48)
Citalopram*	Primary rat astrocytes and neurons	Increased LC3BII/I and Beclin1	no	(52)
Venlafaxine*	Primary rat astrocytes and neurons	No effect	no	(52)
Desipramine*	C6 glioma cells	Inhibition of mTor pathway, increased Beclin1, LC3, autophagosomes	no	(60)
	L929 cells ATG7$^{-/-}$ MEFs	Autophagy induction (LC3II/I up, p62 down,	no	(61)
Nortriptyline*	High content chemical screen in HeLa cells	Autophagy induction (LC3II/I, flux)	yes	(62)
Imipramine*	Glioma cells, mouse models of gliomagenesis	Upregulation of LC3II/I, increased flux, more autophagic vacuoles	Yes (cells)	(63)
	THP-1 cells, depressed patients, ATG5$^{-/-}$MEFs	mRNA of LC3 and Beclin1 up, LC3II/I up	no	(64)
	U-87MG glioma cells	Inhibition of PI3K/Akt/mTOR signaling, LC3II/I up	no	(65)
Maprotiline*	Burkitt's lymphoma cell line	Beclin1 up, more cytoplasmic vacuoles	no	(66)
Mianserin*	THP-1 cells, depressed patients	mRNA of LC3 and Beclin1 up	no	(64)
Mirtazapine*	THP-1 cells, depressed patients, ATG5$^{-/-}$MEFs	mRNA of LC3 and Beclin1 up, LC3II/I up	no	(64)
Fluoxetine*	Human breast cancer cell lines	Upregulation of LC3II/I, Beclin1, ATG5; p62 down	yes	(67)
	Human adipose-derived stem cells, mature adipocytes	Upregulation of LC3II/I, ATG12, SQSTM1, Beclin1, ATG7	no	(68)
	Brain injury in rats	Upregulation of Beclin1, LC3 punctae	no	(69)
	Stress model in rats	Upregulation of Beclin1 and LC3II increased PI3K/Akt/mTOR activity.	no	(43)
	Burkitt's lymphoma cell line	Beclin1 up, more cytoplasmic vacuoles	no	(66)
Sertraline*	Non–small cell lung cancer cells	LC3II up, increased flux, autolysosome formation	yes	(70)
	AML cell lines	LC3II/I increased	no	(71)
Paroxetine*	THP-1 cells, depressed patients	mRNA of LC3 and Beclin1 up	no	(64)
	Mouse stress model, patient blood cells, HEK cells, rat cortical astrocytes	ATG12, LC3II/I, Beclin1, pAkt1 and VPs34 were up, increased flux	yes	(36)
Desvenlafaxine*	THP-1 cells, depressed patients	mRNA of LC3 and Beclin1 up	no	(64)
Agomelatine#	THP-1 cells, depressed patients	mRNA of LC3 and Beclin1 up	no	(64)
Lithium*	ALS mouse model	Increased number of autophagic vacuoles (Beclin1 and LC3)	no	(72)
	Prion-infected cells	LC3II/I and flux increased	yes	(73)
VPA*	Human glioma cell lines	LC3II/I and Beclin1 increased	no	(74)
Ketamine*	Human epithelial cells	LC3II/I and Beclin1 increased	no	(75)
Trehalose	Mouse model of manic-like behaviors	Reduced ratio of p62/beclin1 in the frontal cortex	no	(76)
	Diverse mammalian cells, ATG5$^{-/-}$MEFs	Increased LC3II/I, flux	yes	(77)
Hypericin	Human macrophages	LC3II/I and Beclin1 up, p62 down, only in combination with ultrasound	no	(78)
	Leishmania promastigotes	mRNA of AMPK up, ATGs diversely regulated	no	(79)
Salvianolic acid B	Depression model in rats	Compound restores treatment-induced impairment of autophagy (LC3II/I, Beclin1)	no	(46)
Rosiglitazone*	Depression mouse model, N2a cells, primary neurons	Increases Beclin1, ULK1, LC3II/I, pAMPK, and pAKT1, decreases p62 in stressed mice	no	(45)
Silibinin#	Depression mouse model	Decreased LC3II/I	no	(80)
Dapsone*	Cognition-compromised rats	Enhanced LC3II/I and Beclin1, decreased p62	no	(81)
Geldanamycin	Rat model of anxiety and depression	Atg12, Atg7, and LC3II/I increased	no	(82)
α-tocopherol*	Mouse model of depression	Enhanced LC3II/I, pAMPK decreased p62, pmTOR	no	(44)
Euryale ferox Salisb extracts	Mouse model of depression, HT22 cells	Enhanced LC3II/I, pAMPK decreased p62, pmTOR	no	(83)

**Labels drugs approved by the United States Food and Drug Administration. #Approved in the European Union. LLP, assay to determine the stability of long-lived proteins; DM, double membrane; MEF, mouse embryonic fibroblasts; VPA, valproic acid; AML, acute myeloid leukemia; ALS, amyotrophic lateral sclerosis.*

Experiments employing genetic and pharmacological intervention strategies are needed to finally proof the involvement of functional autophagy in antidepressant action and to disentangle the mechanism including the level of synaptic neurotransmission. More specifically, (conditional) knock-outs of central autophagy genes are available in mice. The high interest in autophagy modulators has led to the discovery of a range of novel autophagy inducers and inhibitors, which can be tested in animal models in depression. While compounds that inhibit autophagy through blocking the fusion between autophagosome

and lysosome frequently elicit toxic effects when applied over a long period of time, they might be useful for assessing the role of autophagy in the immediate actions of antidepressants in some test regimes such as the forced swim test. It will also be interesting to learn whether and how antidepressants can be grouped according to their impact on autophagy. This categorization may not follow the pattern of their mechanism so far known. Finally, it should be investigated whether the dose dependency for autophagy induction by antidepressants is the same as or at least similar to the therapeutic doses.

AUTHOR CONTRIBUTIONS

TR drafted the manuscript. NG added critical information.

FUNDING

This work was partially funded by a NARSAD Young Investigator Award by Brain and Behavior Research Foundation, honored by P&S Fund (to NG, Grant ID 25348).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.