# Autophagy activation as a mechanism of action of psychoactive drugs, revised and expanded version

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April 17, 2023

**Abstract**

Background Autophagy is central to health, and a decline in autophagy from the youthful, healthy state correlates with disease and aging. Among the diseases in which a decline in autophagy is prominent are neurological and neuroimmune disorders, such as Alzheimer's and Parkinson's. Psychiatric disorders are characterized almost universally by increased inflammation and oxidative stress, which are negatively related to levels of autophagy. Treatments designed to restore or increase autophagy may have efficacy in psychiatric disorders such as depression, bipolar disorder, and schizophrenia. Findings Recent research has found that many psychoactive drugs in several different classes, such as anti-psychotics, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and lithium, strongly promote autophagy in neurons. Other diverse interventions, such as rapamycin, trehalose, and exercise, have been shown to have antidepressant effects in animals and sometimes in humans. Most drugs used in other areas of medicine do not activate autophagy. The case is made in this paper that autophagy may play a central role in the mechanism of action of these drugs and interventions through direct effects on autophagy as well as concomitant lowering of levels of inflammation and oxidative stress. Conclusions Many drugs used in the treatment of psychiatric illnesses activate autophagy, and this may be their central mechanism of action, which lends new insight into the pathogenesis of mental illness and to potential new therapies for them.

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BIOLOGICAL SCIENCES

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## ABSTRACT

### BACKGROUND

Autophagy is central to health, and a decline in autophagy from the youthful, healthy state correlates with disease and aging. Among the diseases in which a decline in autophagy is prominent are neurological and neuroimmune disorders, such as Alzheimer's and Parkinson's. Psychiatric disorders are characterized almost universally by increased inflammation and oxidative stress, which are negatively related to levels of autophagy. Treatments designed to restore or increase autophagy may have efficacy in psychiatric disorders such as depression, bipolar disorder, and schizophrenia.

### FINDINGS

Recent research has found that many psychoactive drugs in several different classes, such as anti-psychotics, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and lithium, strongly promote autophagy in neurons. Other diverse interventions, such as rapamycin, trehalose, and exercise, have been shown to have antidepressant effects in animals and sometimes in humans. Most drugs used in other areas of medicine do not activate autophagy. The case is made in this paper that autophagy may play a central role in the mechanism of action of these drugs and interventions through direct effects on autophagy as well as concomitant lowering of levels of inflammation and oxidative stress.

### CONCLUSIONS

Many drugs used in the treatment of psychiatric illnesses activate autophagy, and this may be their central mechanism of action, which lends new insight into the pathogenesis of mental illness and to potential new therapies for them.



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DATE RECEIVED:
June 10, 2015

DOI:
10.15200/winn.143268.86120

ARCHIVED:
May 26, 2015

KEYWORDS:
inflammation, autophagy, psychiatric disorders, antidepressants, oxidative stress

CITATION:

## AUTOPHAGY, HEALTH, AND DISEASE

Autophagy, from the Greek for “self-eating”, is the regulated process of cellular self-cleaning in which poorly functioning organelles, such as mitochondria, and misfolded and glycated proteins, are targeted for destruction. Autophagy declines with age[1] and its decline is prominent in diverse disease states such as heart disease, cancer, and neurodegenerative disorders.[2]

A decline in autophagy is one of a number of cellular and systemic processes seen in aging and illness, and is related to several others, namely increased inflammation, increased oxidative stress, and mitochondrial dysfunction. A number of cellular signaling mechanisms and sensors regulate autophagy, and in turn these mechanisms and sensors feed back and/or activate others, so that, for example, an increase in the level of autophagy contributes to, or coincides with, a decrease in inflammation, oxidative stress, and mitochondrial dysfunction. Among the cellular sensors is mTOR, or mammalian target of rapamycin; inhibition of mTOR increases levels of autophagy. Upstream of mTOR is the growth hormone/IGF-1 system; inhibition of this system, either through lack of IGF-1 receptors, calorie and protein restriction, or lower levels of growth hormones, increases autophagy and is

Dennis Mangan, Autophagy activation as a mechanism of action of psychoactive drugs, revised and expanded version, *The Winnower* 2:e143268.86120 , 2015 , DOI: 10.15200/winn.143268.86120



associated with substantial protection from cancer as well as longer life in laboratory animals.

A further signaling sensor is adenosine monophosphate-activated protein kinase (AMPK), which is at the center of an integrated signaling network that controls aging.[3] Lack of molecular energy in the form of adenosine triphosphate (ATP), as well as a number of chemical compounds such as resveratrol and curcumin, activate AMPK, which in turn inhibits mTOR, causing an increase in autophagy. AMPK also causes a decrease in the activation of NF-kappa B, a transcription factor which increases the production of pro-inflammatory cytokines, thus decreasing systemic inflammation. At the same time, AMPK activates the Nrf2 transcription factor, which causes an increase in phase 2 detoxifying enzymes and in anti-inflammatory cytokines. Activity of AMPK also declines with age, and this is related to an increase in pro-inflammatory cytokines and therefore inflammation and decreased autophagy.

Increased autophagy more directly contributes to a decline in inflammation and oxidative stress by selectively targeting dysfunctional mitochondria, which are the main source of free radicals (reactive oxygen species, ROS) in cells.[4] By breaking down defective mitochondria, autophagy increases mitochondrial turnover and biogenesis, with more of the mitochondria being in their youthful state, and less prone to generate large amounts of ROS.

Autophagy normally proceeds at a low basal rate, and fasting strongly up-regulates it, as do a number of chemical substances, “calorie restriction mimetics”, such as hydroxycitrate, nicotinamide, resveratrol, and epicatechin gallate, a compound found in green tea.[5] The significance here for autophagy enhancers as it relates to drug mechanism and the pathogenesis of mental and neurological disorders is that many autophagy enhancers also extend lifespan in lab animals, so autophagy can be seen as a general health-promoting process, essential to the healthy functioning of the organism, the absence or diminution of which contributes to aging and disease, perhaps including mental illness.

## AUTOPHAGY, INFLAMMATION, AND OXIDATIVE STRESS IN MENTAL ILLNESS

It is now well-established that inflammation and oxidative stress play a substantial, and perhaps even pivotal, role in many mental illnesses, including major depression, bipolar disorder, schizophrenia, and psychotic episodes.

In major depression, the use of selective serotonin uptake inhibitors (SSRIs) results in a remission rate of less than two thirds of patients, which calls into question the serotonin hypothesis of depression. Yet there is ample evidence that depressed patients have increased levels of inflammatory cytokines and increased oxidative stress[6], accompanied by decreased levels of reduced and oxidized glutathione and the enzyme glutathione peroxidase, which uses glutathione to protect against oxidative stress.[7] Indeed, decreased levels of total glutathione characterized post mortem samples of brain tissue in *all* psychiatric disorders.[8] Oxidative stress is increasingly seen as a significant factor in multiple psychiatric disorders.[9] In major depression, inflammation may cause neurodegeneration; factors that predispose toward an increase in inflammation, such as low levels of omega-3 fatty acids or increased intestinal permeability to lipopolysaccharides, are also associated with depression.

Progression of bipolar disorder is also associated with increased inflammation and oxidative stress.[10] Many peripheral biomarkers of oxidative stress and inflammation, such as inflammatory cytokines, are elevated in patients with bipolar disorder, some of them at levels as high as seen in sepsis.[11]

In schizophrenia, inflammation-related genes are up-regulated.[12] Subclinical and chronic inflammation is linked to schizophrenia, and metabolic syndrome and insulin resistance, which increase inflammation, are common among schizophrenics.[13]

In psychosis, genes that regulate the production of pro-inflammatory cytokines are up-regulated.[14] The use of glucocorticosteroids, which decrease inflammation, are associated with substantially and significantly decreased risk for psychosis.[15]

We see that good evidence exists for the presence of increased levels of inflammation and oxidative stress in a number of psychiatric disorders. These processes would be expected to accompany a decrease in autophagy, although evidence for specifically decreased levels of autophagy in mental disorders is indirect. In older people, who would be expected to have aberrant autophagy signaling and decreased basal and activated levels of autophagy, depression is common, and has led to the concept of the “neuroprotective effect of brain reserve” in protection against depression.[16] Much of this brain reserve effect may be due to appropriately regulated mTOR signaling, which mediates autophagy. Rapamycin, which decreases mTOR signaling and increases autophagy, may increase the brain reserve as a buffer against depression.[16]

## MANY PSYCHOACTIVE DRUGS INCREASE AUTOPHAGY

Recent research has found that many psychoactive drugs of different classes used in the treatment of diverse psychiatric disorders activate and increase autophagy in *in vitro* models, and some of them do this quite strongly. It is a striking fact that drugs of diverse classes do this, and this suggests that autophagy activation, along with concomitant decreases in inflammation and oxidative stress, as well as increased quality and quantity of mitochondria, may be related to their mechanism of action. In contrast, most drugs and compounds used in other areas of medicine apparently do not activate autophagy.

Trifluoperazine and chlorpromazine, both anti-psychotic drugs, strongly increased autophagic activity in a neuronal cell culture model, the former by greater than five-fold, the latter by four-fold.[17] In this model, the antihistamine and sedative promethazine also increased autophagy four-fold. Fluspirilene, an antipsychotic used in the treatment of schizophrenia, doubled autophagic activity, while quinacrine, a drug used as an anti-protozoal, had no effect on autohagy.

In a model system using rat primary astrocytes and neurons, it was found that the antidepressant drugs amitryptilene, a tricyclic, and citalopram, an SSRI, both increased autophagy.[18] In the same model, however, venlaxafine, an SSRI that also inhibits norepinephrine reuptake, did not activate autophagy.

The SSRI fluoxetine promotes autophagy in a chemoresistant Burke's lymphoma cell line, as does the tetracyclic antidepressant maprotiline.[19] The widely used anticonvulsant and mood stabilizer valproic acid induces autophagy in a glioma cell line.[20]

Lithium has been used in the treatment of bipolar disorder and depression for decades, and is of yet another different class of compound, a mineral salt. Lithium extends life in metazoans, and it is associated with increased lifespan in humans.[21] Lithium induces autophagy by an mTOR-independent mechanism, through the inhibition of inositol monophosphatase.[22] This is likely to be its mechanism of action in extending lifespan, though whether autophagy is involved in its alleviation of bipolar disorder remains to be seen; doses used in bipolar disorder are hundreds fold higher than those that extend lifespan.

It can be seen that a number of members of varied classes of psychoactive compounds, such as tricyclics, SSRIs, a mineral salt, and antipsychotics, activate autophagy, some of them quite strongly. In contrast, most chemical compounds apparently do not activate autophagy. For example, the Prestwick Chemical Library is a collection of 1,280 compounds that have been approved for human use by the FDA, EMA, and other agencies. This collection was specifically designed for screening purposes and to produce a low number of non-hits. In a screening for autophagic activity of 1,120 of FDA-approved compounds from the Prestwick Chemical Library, only 38 of them were identified as potential activators of autophagy.[23] Interestingly, among the potential autophagy activators was the SSRI paroxetine.

In a screening of 50,729 small molecular compounds for ability to inhibit mTOR and enhance autophagy, only 3 were found that were both non-toxic and induced autophagy in mammalian cells.[24] Both of these examples of the screening of large numbers of drugs and chemical compounds for their

ability to enhance or induce autophagy and the finding of only a few, stand in stark contrast to the number of psychoactive drugs that promote autophagy. The difference seems unlikely to be due to chance alone.

## AUTOPHAGY ACTIVATORS HAVE PSYCHOACTIVE AND NEURONAL EFFECTS

In contrast to the seemingly very low rate of autophagy enhancers among both FDA-approved drugs and a large array of small molecular compounds, a number of interventions, both chemical and otherwise, that are known to induce autophagy also have antidepressant or other psychoactive effects in animal models, and sometimes in humans.

Rapamycin, an immunosuppressant which is well-known as an inhibitor of mTOR and which strongly activates autophagy, has antidepressant effects in rats and mice.[25]

The disaccharide trehalose, which activates autophagy and which extends the lifespan of the nematode *C. elegans*[26], has antidepressant effects in a mouse model.[27]

Exercise has an antidepressant effect in humans[28], and up-regulation of autophagy appears to be critical to the beneficial health effects of exercise.[29]

Resveratrol activates AMPK and thus increases autophagy.[30] It also has an antidepressant effect in a mouse model.[31]

The very low carbohydrate ketogenic diet (VLCKD) has a decades-long successful record in the treatment of refractory epilepsy.[32] While the precise anticonvulsant mechanism of the VLCKD in epilepsy is unknown, increased mitochondrial biogenesis and enhanced brain metabolism are thought to play a role.[33] Autophagy induces or enhances mitochondrial biogenesis, and the VLCKD also induces autophagy.[34] In addition, an intervention which produces ketone bodies, fasting, causes profound neuronal autophagy.[35] There is some indication that ketogenic diets may be useful in the treatment of schizophrenia. [36.]

We see that five interventions or compounds of disparate classes that are not psychoactive drugs, from an immunosuppressant to a sugar to a polyphenol to physical activity to a ketogenic diet, both activate autophagy and have antidepressant or other psychoactive or neuronal effects in humans or animal models.

## CONCLUSIONS

We have seen that a wide array of psychoactive drugs from diverse classes induce or activate autophagy, the disregulation of which is prominent in a number of disease states. Regulation of autophagy is intertwined with various cellular sensors that also affect control of inflammation and oxidative stress. Hence, autophagy could be central to some of these drugs' mechanism of action either by the increase of autophagy itself, or by the concomitant decrease in inflammation and oxidative stress, which are increasingly thought to play a pivotal role in neurological and psychiatric disorders.

So far as is known, the proportion of FDA-approved compounds and small molecules that induce or enhance autophagy is small, much smaller than that found in psychoactive drugs. This lends some additional support to the notion that autophagy is important to the efficacy of psychoactive drugs used in the treatment of mental illness. Other interventions and compounds, such as exercise, rapamycin, trehalose, resveratrol, and the ketogenic diet, activate autophagy and have antidepressant or other psychoactive and neuronal effects in animal models and in some cases in humans.

Further research is needed on the effects on autophagy of psychoactive drugs. Most of the effects seem so far to have been discovered almost by chance; a systematic screening of psychoactive drugs for autophagic activity may be useful and may help to clarify whether and how much autophagy plays a role in psychiatric disorders.

The putative role of autophagy activation in the effects of psychoactive drugs lends further evidence to the centrality of inflammation and oxidative stress, and perhaps autophagy itself, in mental illness.

## ABBREVIATIONS

mTOR: mammalian target of rapamycin

AMPK: adenosine monophosphate-activated protein kinase

ATP: adenosine triphosphate

SSRI: selective serotonin reuptake inhibitor

ROS: reactive oxygen species

FDA: Food and Drug Administration

EMA: European Medicines Agency

VLCKD: very low carbohydrate ketogenic diet

Competing Interests: The author declares that he has no competing interests.

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