



Autophagy as mechanism of action of psychoactive drugs

P. D. MANGAN

READ REVIEWS

WRITE A REVIEW

CORRESPONDENCE:

dennis_mangan@hotmail.com

DATE RECEIVED:

June 10, 2015

© Mangan This article is distributed under the terms of the [Creative Commons Attribution 4.0 International License](#), which permits unrestricted use, distribution, and redistribution in any medium, provided that the original author and source are credited.



Autophagy, literally “self-eating”, is the regulated process of cellular self-cleaning in which poorly functioning organelles, such as mitochondria, and misfolded proteins, are targeted for destruction. Autophagy declines with age¹ and its decline is prominent in diverse disease states such as heart disease, cancer, and neurodegenerative disorders.²

Autophagy is tightly regulated by a number of physiological sensors and hormones, such as mTOR, AMPK, and the growth hormone/IGF-1 axis. Processes and chemical compounds that increase the activity of AMPK increase the level of autophagy in a cell, and in turn, the Nrf2 transcription factor is upregulated, causing an increase in transcription of antioxidant enzymes and a decrease in transcription of pro-inflammatory cytokines.³ Activity of AMPK also declines with age, and this is related to an increase in pro-inflammatory cytokines and therefore inflammation.

Autophagy itself causes a decline in levels of inflammation by reducing the numbers of defective mitochondria, which are important generators of inflammatory signaling.⁴ Increased levels of autophagy result in decreased levels of inflammatory cytokines and inflammation.

Many psychoactive drugs used in the treatment of several mental illnesses activate autophagy, some of them quite strongly. A number of anti-psychotic drugs, including trifluoperazine and chlorpromazine, increased autophagy in an *in vitro* neuronal cell culture model four-fold, as did the antihistamine and sedative promethazine.⁵ Other psychoactive drugs in this model also increased autophagy, although not as strongly, and a few showed no increase.

Lithium has been used for decades in the treatment of bipolar disorder and in depression. Recently, it's been found that lithium increases lifespan in the nematode *C. elegans*, and lithium in drinking water is associated with increased lifespan in humans.⁶ Lithium promotes autophagy in an mTOR-independent manner⁷, and this is likely to be its mechanism of action in extending lifespan in *C. elegans*.

Selective serotonin reuptake inhibitors (SSRIs) are used in the treatment of depression. At least one SSRI, citalopram, has been found to increase autophagy in neurons.⁸

We have evidence that representatives of four classes of psychoactive drugs, anti-psychotics, tricyclic antidepressants, lithium, and SSRIs, promote autophagy. Could this be, at least in part, their mechanism of action?

It's now well-established that inflammatory processes play a substantial, perhaps even pivotal, role in depression.⁹ Inflammation is thought to lead to neurodegeneration, which is also seen in depression. In schizophrenia, inflammatory genes are upregulated.¹⁰ Inflammation also appears to be crucial in the

pathogenesis of bipolar disorder.¹¹

Psychoactive drugs used to treat depression, psychosis, and bipolar disorder may owe some of their efficacy to their ability to increase levels of autophagy. At the least, it's a striking fact that representative drugs from different classes of psychoactive compounds do this. Rapamycin, an immunosuppressant of an entirely different class that inhibits mTOR, increases autophagy, and increases lifespan in mice, also has antidepressant effects.¹² Yet in a recent study that screened 1,120 FDA-approved compounds for inducing autophagy, only 38 compounds were found to be potential autophagy activators.¹³

Autophagy activators can be expected to reduce inflammation and oxidative stress, and increase energy generation in neurons, and this could be their mechanism of action in mental illness.

1. Rubinsztein, David C., Guillermo Mariño, and Guido Kroemer. "Autophagy and aging." *Cell* 146, no. 5 (2011): 682-695.
2. Levine, Beth, and Guido Kroemer. "Autophagy in the pathogenesis of disease." *Cell* 132, no. 1 (2008): 27-42.
3. Salminen, Antero, and Kai Kaarniranta. "AMP-activated protein kinase (AMPK) controls the aging process via an integrated signaling network." *Ageing research reviews* 11, no. 2 (2012): 230-241.
4. Green, Douglas R., Lorenzo Galluzzi, and Guido Kroemer. "Mitochondria and the autophagy–inflammation–cell death axis in organismal aging." *Science* 333, no. 6046 (2011): 1109-1112.
5. Tsvetkov, Andrey S., Jason Miller, Montserrat Arrasate, Jinny S. Wong, Michael A. Pleiss, and Steven Finkbeiner. "A small-molecule scaffold induces autophagy in primary neurons and protects against toxicity in a Huntington disease model." *Proceedings of the National Academy of Sciences* 107, no. 39 (2010): 16982-16987.
6. Zarse, Kim, et al. "Low-dose lithium uptake promotes longevity in humans and metazoans." *European journal of nutrition* 50.5 (2011): 387-389.
7. Sarkar, Sovan, R. Andres Floto, Zdenek Berger, Sara Imarisio, Axelle Cordenier, Matthieu Pasco, Lynnette J. Cook, and David C. Rubinsztein. "Lithium induces autophagy by inhibiting inositol monophosphatase." *The Journal of cell biology* 170, no. 7 (2005): 1101-1111.
8. Zschocke, Jürgen, et al. "Antidepressant drugs diversely affect autophagy pathways in astrocytes and neurons—dissociation from cholesterol homeostasis." *Neuropsychopharmacology* 36.8 (2011): 1754-1768.
9. Maes, Michael, Raz Yirmiya, Jens Norberg, Stefan Brene, Joe Hibbeln, Giulia Perini, Marta Kubera, Petr Bob, Bernard Lerer, and Mario Maj. "The inflammatory & neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depression." *Metabolic brain disease* 24, no. 1 (2009): 27-53.
10. Saetre, Peter, Lina Emilsson, Elin Axelsson, Johan Kreuger, Eva Lindholm, and Elena Jazin. "Inflammation-related genes up-regulated in schizophrenia brains." *Bmc Psychiatry* 7, no. 1 (2007): 46.
11. Berk, Michael, et al. "Pathways underlying neuroprogression in bipolar disorder: focus on inflammation, oxidative stress and neurotrophic factors." *Neuroscience & biobehavioral reviews* 35.3 (2011): 804-817.
12. Cleary, C., J. A. S. Linde, K. M. Hiscock, I. Hadas, R. H. Belmaker, G. Agam, S. Flaisher-Grinberg, and H. Einat. "Antidepressive-like effects of rapamycin in animal models: Implications for mTOR inhibition as a new target for treatment of affective disorders." *Brain research bulletin* 76, no. 5 (2008): 469-473.
13. Hundeshagen, Phillip, Anne Hamacher-Brady, Roland Eils, and Nathan R. Brady. "Concurrent detection of autolysosome formation and lysosomal degradation by flow cytometry in a high-content screen for inducers of autophagy." *BMC biology* 9, no. 1 (2011): 38.