Journal of Integrative Neuroscience

J. Integr. Neurosci. **2025**; 24(7): 41820
https://doi.org/10.31083/JIN41820

Editorial

LHb Neuronal Autophagy: A Central Mechanism in the Stress Response

Zi-Cun Liu[1], Jian-Guo Chen[1,2], Fang Wang[1,2,*]

[1]Department of Pharmacology, School of Basic Medicine, Tongji Medical College, Huazhong University of Science and Technology, 430030 Wuhan, Hubei, China
[2]The Research Center for Depression, Tongji Medical College, Huazhong University of Science and Technology, 430030 Wuhan, Hubei, China
*Correspondence: Wangfangtj0322@163.com (Fang Wang)

Academic Editor: Bettina Platt
Submitted: 20 May 2025 Revised: 3 June 2025 Accepted: 10 June 2025 Published: 25 July 2025

Autophagy, a critical mechanism for maintaining cellular homeostasis, participates in the growth and refinement of neuronal axons, dendrites, and synapses in both the developing and adult brain [1]. In a groundbreaking study published in Nature, Yang *et al*. [2] found that stress modulated depression via dynamic control of neuronal autophagy in the lateral habenula (LHb). The authors showed that LHb autophagy regulated neuronal excitability and synaptic plasticity through activity-dependent clearance of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors to maintain emotional homeostasis against stress, thereby identifying an entirely new avenue for therapeutic development in major depressive disorder (MDD).

Depression indicates a dysregulated stress response, during which the brain undergoes three progressive phases: alarm reaction, resistance, and exhaustion [3]. A key consequence of stress is structural remodeling of neural architecture; recovery from these changes reflects successful regulation of homeostasis, whereas persistence indicates failed resilience [4]. The cumulative pathophysiology resulting from such dysregulation and excess stress may contribute to neuropsychiatric disorders including MDD. Autophagy is recognized as a critical homeostatic regulator: mutations in autophagy genes cause congenital neurological disorders (e.g., epilepsy, intellectual disability, neurodegeneration); and functional deficiency leads to motor dysfunction, cognitive impairment, social deficits, and seizures, which are associated with impaired synaptic maturation, plasticity and neurotransmission [5]. Accumulating evidence has demonstrated that functional restoration of impaired autophagic components, such as p62, nuclear receptor binding factor 2, and nineteen-kilodalton Interacting Protein-3-like protein X (NIX), in depression models, ameliorates depressive-like phenotypes through distinct molecular mechanisms [6–8]. The LHb, being a stress-vulnerable target, exhibits hyperactivity, synaptic protein dysregulation and compromised neuronal homeostasis under chronic stress [9]. The study found a causal role of LHb autophagy in coping with stress.

Yang *et al*. [2] found that chronic stress impaired LHb autophagy, and both paroxetine and ketamine selectively increased autophagic activity specifically in LHb, without affecting other depression-associated brain regions. It is interesting that the authors further found that acute and chronic stress had opposite effects on autophagy: acute stress activated 5′-adenosine-monophosphate-activated-protein-kinase (AMPK) to initiate LHb autophagy, whereas chronic stress activated mammalian target of rapamycin (mTOR) to terminate LHb autophagy. Recent evidence has demonstrated that antidepressants exert therapeutic effects through diverse mechanisms, with substantial heterogeneity observed even in their autophagy-mediated actions [10,11]. Critically, that same study revealed that multiple antidepressants required LHb autophagy activation to ameliorate depression-like phenotypes in chronically stressed mice by normalizing both neuronal hyperactivity and synaptic deficits. These findings suggest that chronic stress induces physiological structural alterations through LHb autophagic impairment, whereas pharmacological activation of LHb autophagy reestablishes neuronal homeostasis. This identifies LHb autophagy as a critical regulator of neuronal homeostasis. Based on the distinct effects of acute and chronic stress on LHb autophagy, this study proposed a stress-phase-dependent regulatory mechanism by which LHb autophagy maintains neuronal homeostasis: (a) acute stress activates LHb autophagy via AMPK signaling (alarm phase); (b) sustained stress potentiates LHb excitatory inputs, requiring persistent autophagy to degrade excess AMPA receptors (resistance phase); and (c) in chronic stress, mTOR-mediated autophagy suppression prevents AMPA receptors clearance, leading to synaptic overload and depression-like phenotypes (exhaustion phase).

To elucidate the neuronal mechanisms underlying depression-like behaviors caused by impaired LHb neuronal autophagy, the authors employed a dual-viral approach to monitor stress-induced calcium responses in autophagy-deficient LHb neurons. Genetic elimination of LHb neuronal autophagy directly elicited depression-like phenotypes, neuronal hyperexcitability, and exaggerated calcium responses to diverse stressors. Genetic elimination of LHb neuronal autophagy can be interpreted as disrup-

tion of a crucial homeostatic mechanism, functionally eliminating the resistance phase of the stress response. Given that LHb hyperactivity is a cellular hallmark of depression-like status, the authors used a dual viral strategy to silence autophagy-deficient LHb neurons chemogenetically, which successfully alleviated depression-like behaviors in autophagy-deficient mice. These results indicate that LHb hyperactivity constitutes the cellular substrate underlying the depression-like phenotype induced by impaired LHb autophagy. Although this study demonstrated that autophagy-gated depression-like states are localized to specific brain regions and cell types, autophagy regulates not only neuronal homeostasis but also metabolic and immune homeostasis [12]. During stress adaptation, the autonomic nervous system, metabolic system, and immune system engage in dynamic nonlinear crosstalk to orchestrate cerebral homeostasis [4]. The effects of autophagy on metabolic and immune homeostasis cannot be ignored in mechanistic research on depression. Although this study established that autophagy deficiency in either LHb astrocytes or ventral hippocampal neurons does not produce behavioral effects, the potential role of glial autophagy in stress-related depression remains significant given two key mechanisms: astrocytic regulation of neuronal metabolic support; and microglial control of neuroinflammation [13,14]. Future investigations should explore whether stress-induced disruptions of astrocytic autophagy impair metabolic homeostasis, or whether dysregulation of autophagy in astrocyte and microglia influences depression-like behaviors through neuroimmune mechanisms.

LHb autophagy controls neuronal excitability, synaptic transmission (by means of on-demand degradation of glutamate receptors), and critically contributes to synaptic plasticity, particularly long-term depression (LTD). Here, the authors established a causal relationship between LHb autophagy activation and LTD induction; the blockade of LHb autophagy led to excessive accumulation of post-synaptic AMPA receptors during long-term potentiation induction. Together, these findings established that autophagy in LHb neurons critically regulates both the frequency and amplitude of synaptic plasticity events. Neurons in the neocortex typically adjust the strength of excitatory synapses to maintain activity around a homeostatic set point [15]. These findings demonstrated that LHb neuronal autophagy regulates excitatory synaptic homeostasis, suggesting its potential in maintaining brain balance through homeostatic regulation of network function.

Again, depression indicates a dysregulated stress response, during which the brain undergoes three progressive phases: alarm reaction, resistance, and exhaustion. Critically, the prevention of depression and the action of antidepressants rely on regulatory mechanisms that maintain brain homeostasis during the resistance phase. This study determined the mechanism of synaptic adaptability in the LHb that dynamic regulation of surface AMPA receptor levels by autophagy mechanisms of synaptic adaptability in the LHb. The selective modulation of LHb autophagy by stress and antidepressants implies that stress exerts spatially and cellularly restricted control over autophagic processes. Such regulation may reflect functional diversification of autophagy, wherein distinct autophagic programs orchestrate discrete aspects of brain homeostasis.

Author Contributions

FW and JGC: Writing and Supervision. ZCL: Original draft. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest. Fang Wang is serving as one of the Editorial Board members of this journal. We declare that Fang Wang had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Bettina Platt.

References

[1] Zhou Y, Nan F, Zhang Q, Xu W, Fang S, Liu K, *et al*. Natural products that alleviate depression: The putative role of autophagy. Pharmacology & Therapeutics. 2024; 264: 108731. https://doi.org/10.1016/j.pharmthera.2024.108731.

[2] Yang L, Guo C, Zheng Z, Dong Y, Xie Q, Lv Z, *et al*. Stress dynamically modulates neuronal autophagy to gate depression onset. Nature. 2025; 641: 427–437. https://doi.org/10.1038/s41586-025-08807-4.

[3] Gold PW, Wong ML. Advances in discerning the mechanisms underlying depression and resiliency: relation to the neurobiology of stress and the effects of antidepressants. Molecular Psychiatry. 2025. https://doi.org/10.1038/s41380-025-03019-8. (online ahead of print)

[4] McEwen BS, Bowles NP, Gray JD, Hill MN, Hunter RG, Karatsoreos IN, *et al*. Mechanisms of stress in the brain. Nature Neuroscience. 2015; 18: 1353–1363. https://doi.org/10.1038/nn.4086.

[5] Karpova A, Hiesinger PR, Kuijpers M, Albrecht A, Kirstein J, Andres-Alonso M, *et al*. Neuronal autophagy in the control of synapse function. Neuron. 2025; 113: 974–990. https://doi.org/10.1016/j.neuron.2025.01.019.

[6] Seibenhener ML, Zhao T, Du Y, Calderilla-Barbosa L, Yan J, Jiang J, *et al*. Behavioral effects of SQSTM1/p62 overexpression in mice: support for a mitochondrial role in depression

and anxiety. Behavioural Brain Research. 2013; 248: 94–103. https://doi.org/10.1016/j.bbr.2013.04.006.

[7] Zhang SQ, Deng Q, Zhu Q, Hu ZL, Long LH, Wu PF, *et al*. Cell type-specific NRBF2 orchestrates autophagic flux and adult hippocampal neurogenesis in chronic stress-induced depression. Cell Discovery. 2023; 9: 90. https://doi.org/10.1038/s41421-023-00583-7.

[8] Lu JJ, Wu PF, He JG, Li YK, Long LH, Yao XP, *et al*. BNIP3L/NIX-mediated mitophagy alleviates passive stress-coping behaviors induced by tumor necrosis factor-α. Molecular Psychiatry. 2023; 28: 5062–5076. https://doi.org/10.1038/s41380-023-02008-z.

[9] Zheng Z, Liu Y, Mu R, Guo X, Feng Y, Guo C, *et al*. A small population of stress-responsive neurons in the hypothalamus-habenula circuit mediates development of depression-like behavior in mice. Neuron. 2024; 112: 3924–3939.e5. https://doi.org/10.1016/j.neuron.2024.09.012.

[10] Hwang HY, Shim JS, Kim D, Kwon HJ. Antidepressant drug sertraline modulates AMPK-MTOR signaling-mediated autophagy via targeting mitochondrial VDAC1 protein. Autophagy. 2021; 17: 2783–2799. https://doi.org/10.1080/15548627.2020.1841953.

[11] Alcocer-Gómez E, Casas-Barquero N, Williams MR, Romero-Guillena SL, Cañadas-Lozano D, Bullón P, *et al*. Antidepressants induce autophagy dependent-NLRP3-inflammasome inhibition in Major depressive disorder. Pharmacological Research. 2017; 121: 114–121. https://doi.org/10.1016/j.phrs.2017.04.028.

[12] Clarke AJ, Simon AK. Autophagy in the renewal, differentiation and homeostasis of immune cells. Nature Reviews. Immunology. 2019; 19: 170–183. https://doi.org/10.1038/s41577-018-0095-2.

[13] Beard E, Lengacher S, Dias S, Magistretti PJ, Finsterwald C. Astrocytes as Key Regulators of Brain Energy Metabolism: New Therapeutic Perspectives. Frontiers in Physiology. 2021; 12: 825816. https://doi.org/10.3389/fphys.2021.825816.

[14] Tang M, Liu T, Jiang P, Dang R. The interaction between autophagy and neuroinflammation in major depressive disorder: From pathophysiology to therapeutic implications. Pharmacological Research. 2021; 168: 105586. https://doi.org/10.1016/j.phrs.2021.105586.

[15] Wen W, Turrigiano GG. Keeping Your Brain in Balance: Homeostatic Regulation of Network Function. Annual Review of Neuroscience. 2024; 47: 41–61. https://doi.org/10.1146/annurev-neuro-092523-110001.