Press Release

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New Clues to the Mechanism Behind Treatment-Resistant Depression

New animal model study in Biological Psychiatry identified gene that interacts with stress

Philadelphia, November 2, 2023 – Major depressive disorder (MDD) is a widespread mental health condition that for many is disabling. It has long been appreciated that MDD has genetic as well as environmental influences. In a new study in *Biological Psychiatry*, published by Elsevier, researchers identify a gene that interacted with stress to mediate aspects of treatment-resistant MDD in an animal model.

Jing Zhang, PhD, at Fujian Medical University and senior author of the study, said, "*Emerging evidence suggests that MDD is a consequence of the co-work of genetic risks and environmental factors, so it is crucial to explore how stress exposure and risk genes co-contribute to the pathogenesis of MDD."*

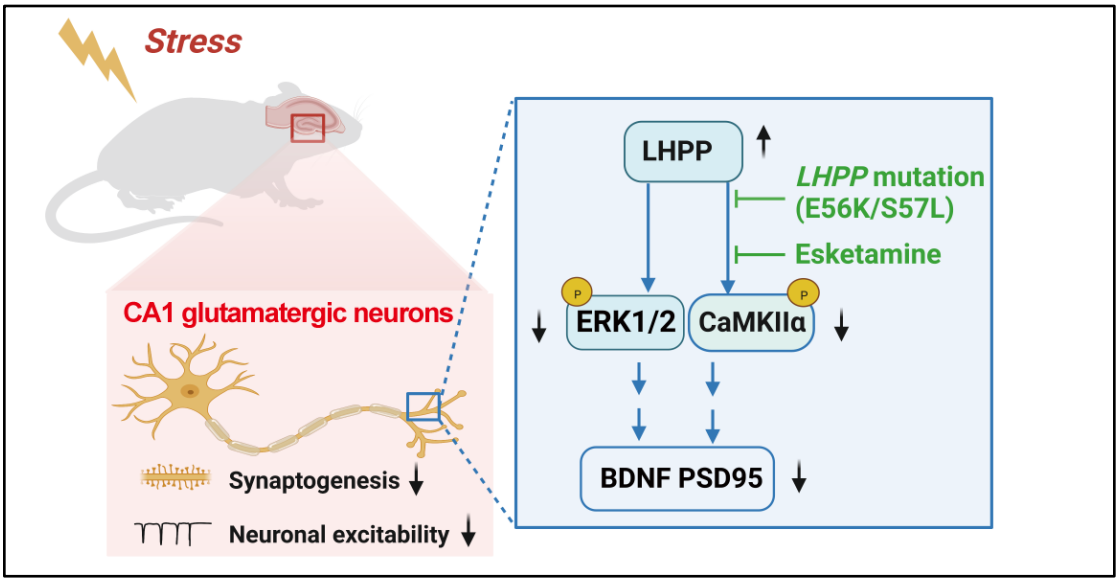
To do that, the authors used a mouse model of stress-induced depression called chronic social defeat stress (CSDS) in which mice are exposed to aggressor mice daily for two weeks. They focused on a gene called *LHPP*, which interacts with other signaling molecules at neuronal synapses. Increased expression of LHPP in the stressed mice aggravated the depression-like behaviors by decreasing expression of BDNF and PSD95 by dephosphorylating two protein kinases, CaMKIIα and ERK, under stress exposure.

Dr. Zhang noted, "*Interestingly,* LHPP *mutations (E56K, S57L) in humans can enhance CaMKIIα/ERK-BDNF/PSD95 signaling, which suggests that carrying* LHPP *mutations may have an antidepressant effect in the population."*

MDD is an extremely heterogeneous condition. Differences in the types of depression experienced by people influence the way they respond to treatment. A large subgroup of people with depression fail to respond to standard antidepressant medications and have "treatment-resistant" symptoms of depression. These patients often respond to different medications, such as ketamine or esketamine, or to electroconvulsive therapy. Notably, esketamine markedly alleviated LHPP-induced depression-like behaviors, whereas the traditional drug fluoxetine did not, suggesting that the mechanism might underlie some types of treatment-resistant depression.

John Krystal, MD, Editor of *Biological Psychiatry*, said of the work, *"We have limited understanding of the neurobiology of treatment-resistant forms of depression. This study identifies a depression risk mechanism for stress-related behaviors that fail to respond to a standard antidepressant but respond well to ketamine. This may suggest that the risk mechanisms associated with the* LHPP *gene shed light on the poorly understood biology of treatment-resistant forms of depression."*

Dr. Zhang added, *"Together, our findings identify LHPP as an essential player driving stress-induced depression, implying targeting LHPP as an effective strategy in MDD therapeutics in the future."*



Caption: In a new study in *Biological Psychiatry* researchers identified a gene that interacted with stress to mediate aspects of treatment-resistant major depressive disorder in an animal model (Credit: *Biological Psychiatry*).

Notes for editors

The article is "LHPP in glutamatergic neurons of the ventral hippocampus mediates depression-like behavior by dephosphorylating CaMKIIα and ERK," by Lvping Zhuang, Weijie Gao, Yanbing Chen, Wenting Fang, Hsuan Lo, Xiaoman Dai, Jie Zhang, Wanjing Chen, Qinyong Ye, Xiaochun Chen, and Jing Zhang (https://doi.org/10.1016/j.biopsych.2023.08.026). It appears as an Article in Press in *Biological Psychiatry*, published by Elsevier.

Copies of this paper are available to credentialed journalists upon request; please contact Rhiannon Bugno at Biol.Psych@sobp.org. Journalists wishing to interview the authors may contact Jing Zhang, PhD, at +8613905910511 or drzj@fjmu.edu.cn, or Xiaochun Chen, PhD, at +8613905016998 or chenxc998@163.com.

The authors' affiliations and disclosures of financial and conflicts of interests are available in the article.

John H. Krystal, MD, is Chairman of the Department of Psychiatry at the Yale University School of Medicine, Chief of Psychiatry at Yale-New Haven Hospital, and a research psychiatrist at the VA Connecticut Healthcare System. His disclosures of financial and conflicts of interests are available here.

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Biological Psychiatry is the official journal of the Society of Biological Psychiatry, whose purpose is to promote excellence in scientific research and education in fields that investigate the nature, causes, mechanisms and treatments of disorders of thought, emotion, or behavior. In accord with this mission, this peer-reviewed, rapid-publication, international journal publishes both basic and clinical contributions from all disciplines and research areas relevant to the pathophysiology and treatment of major psychiatric disorders.

The journal publishes novel results of original research which represent an important new lead or significant impact on the field, particularly those addressing genetic and environmental risk factors, neural circuitry and neurochemistry, and important new therapeutic approaches. Reviews and commentaries that focus on topics of current research and interest are also encouraged.

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