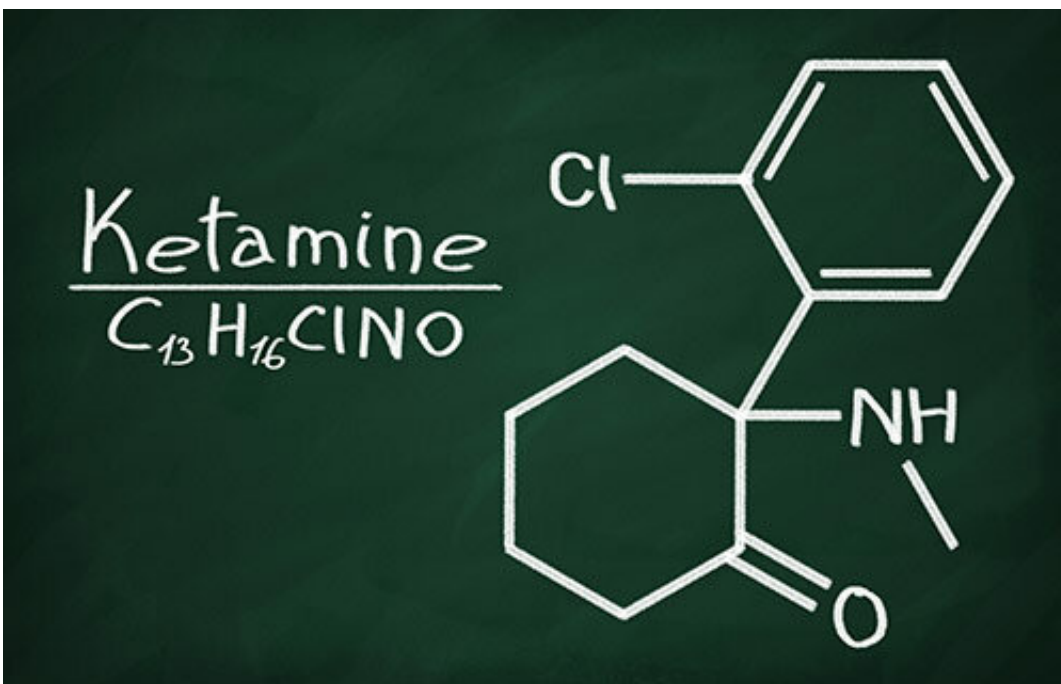


Researchers discover a critical receptor involved in response to antidepressants like ketamine

March 28 2019, by Joanne Morrison



Ketamine structural model. Credit: University of Maryland School of Medicine

Effective treatment of clinical depression remains a major mental health issue, with roughly 30 percent of patients who do not respond to any of the available treatments. Researchers at the University of Maryland School of Medicine (UMSOM) have discovered a crucial receptor called mGlu2 that is critical to the mechanism of fast-acting antidepressants

such as ketamine when used to treat depression.

This discovery into how this type of receptor in the brain works with fast-acting antidepressants is a critical discovery in treating [depression](#), because existing treatments can take weeks before they are effective. A single dose of [ketamine](#) that is lower than the amount required to cause anesthesia within 24 hours can alleviate depression in some [treatment](#)-resistant patients.

Todd Gould, MD., Associate Professor in the Department of Psychiatry, together with researchers from the National Institutes of Health Intramural Research Program, discovered that this special type of glutamate receptor interacts with ketamine's mechanism.

"Understanding the neurological response to antidepressants such as ketamine help us better understand depression and how to best treat this serious disease," said Dr. Gould.

The effects of ketamine can last up to a few weeks. And while it is a fast-acting treatment for depression, it is not an ideal treatment because it can alter sensory perception and has a high potential for abuse. Thus, there is a tremendous need to identify the mechanisms through which ketamine mediates its antidepressant effects to help identify alternative drugs that more specifically enhance the pathway in the brain that is suppressed in depressed patients.

Necessary Receptors

Dr. Gould's research, which was conducted in mice, showed that the mGlu2 receptor is necessary of the antidepressant activity of ketamine, and the ketamine metabolite. Researchers were able to uncover the important role this receptor plays in ketamine effectiveness by removing the gene for this receptor in mice, which in turn blocked the

antidepressant effects of fast-acting treatment. Additionally, Dr. Gould's research provided evidence that an increase in a particular form of brain activity, measured by quantitative EEG, can be used as an indicator of on-target activity of fast-acting antidepressants.

The researchers used mice to determine that (2R, 6R)-HNK's mechanism of action involved mGlu2 [receptors](#). Various experimental strategies were applied, including pharmacological manipulation of mGlu2 activity, genetic knockout of the mGlu2-encoding gene, behavioral tests, and cortical EEG measurements.

"Having a better understanding of how the brain reacts to Ketamine is a critical pathway toward advancing treatment of Depression," said UMSOM Dean E. Albert Reece, MD, Ph.D., MBA, who is also the Executive Vice President for Medical Affairs, University of Maryland, and the John Z. and Akiko K. Bowers Distinguished Professor.

More information: Panos Zanos et al, (2R,6R)-hydroxynorketamine exerts mGlu2receptor-dependent antidepressant actions, *Proceedings of the National Academy of Sciences* (2019). [DOI: 10.1073/pnas.1819540116](#)

Provided by University of Maryland School of Medicine

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