Ketamine reverses neural changes underlying depression-related behaviors in mice

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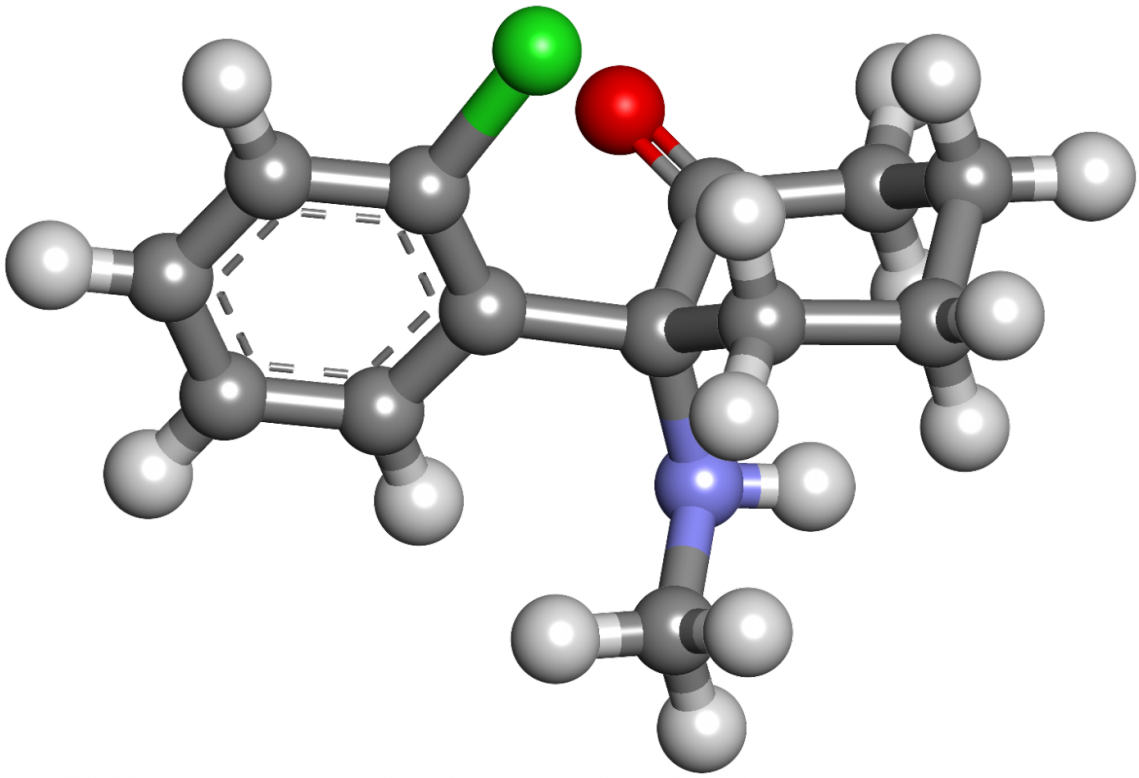

3D model of Ketamine. Credit: Wikipedia

Researchers have identified ketamine-induced brain-related changes that are responsible for maintaining the remission of behaviors related to

depression in mice—findings that may help researchers develop interventions that promote lasting remission of depression in humans. The study, funded by the National Institute of Mental Health (NIMH), part of the National Institutes of Health, appears in the journal *Science*.

Major depression is one of the most common mental disorders in the United States, with approximately 17.3 million adults experienced a major depressive episode in 2017. However, many of the neural changes underlying the transitions between active depression, remission, and depression re-occurrence remain unknown. Ketamine, a fast-acting antidepressant which relieves depressive symptoms in hours instead of weeks or longer, provides an opportunity for researchers to investigate the short- and long-term biological changes underlying these transitions.

"Ketamine is a potentially transformative treatment for depression, but one of the major challenges associated with this drug is sustaining recovery after the initial treatment," said study author Conor Liston, M.D., Ph.D., of Weill Cornell Medicine, New York City.

To understand mechanisms underlying the transition from active depression to remission in humans, the researchers examined behaviors related to depression in mice. Researchers took high-resolution images of dendritic spines in the prefrontal cortex of mice before and after they experienced a stressor. Dendritic spines are protrusions in the part of neurons that receive communication input from other neurons. The researchers found that mice displaying behaviors related to depression had increased elimination of, and decreased formation of, dendritic spines in their prefrontal cortex compared with mice not exposed to a stressor. This finding replicates prior studies linking the emergence of behaviors related to depression in mice with dendritic spine loss.

In addition to the effects on dendritic spines, stress reduced the functional connectivity and simultaneous activity of neurons in the

prefrontal cortex of mice. This reduction in connectivity and activity was associated with behaviors related to depression in response to stressors. Liston's group then found that ketamine treatment rapidly restored functional connectivity and ensemble activity of neurons and eliminated behaviors related to depression. Twenty-four hours after receiving a single dose of ketamine, mice exposed to stress showed a reversal of behaviors related to depression and an increase in dendritic spine formation when compared to stressed mice that had not received ketamine. These new dendritic spines were functional, creating working connections with other neurons.

The researchers found that while behavioral changes and changes in neural activity in mice happened quickly (three hours after ketamine treatment), dendritic spine formation happened more slowly (12-24 after hours after ketamine treatment). While further research is needed, the authors suggest these findings might indicate that dendritic spine regrowth may be a consequence of ketamine-induced rescue of prefrontal cortex circuit activity.

Although dendritic spines were not found to underly the fast-acting effects of ketamine on behaviors related to depression in mice, they were found to play an important role in maintaining the remission of those behaviors. Using a new technology developed by Haruo Kasai, Ph.D., and Haruhiko Bito, Ph.D., collaborators at the University of Tokyo, the researchers found that selectively deleting these newly formed dendritic spines led to the re-emergence of behaviors related to depression.

"Our results suggest that interventions aimed at enhancing synapse formation and prolonging their survival could be useful for maintaining the antidepressant effects of ketamine in the days and weeks after treatment," said Dr. Liston.

"Ketamine is the first new anti-depressant medication with a novel mechanism of action since the 1980s. Its ability to rapidly decrease suicidal thoughts is already a fundamental breakthrough," said Janine Simmons, M.D., Ph.D., chief of the NIMH Social and Affective Neuroscience Program. "Additional insights into ketamine's longer-term effects on brain circuits could guide future advances in the management of mood disorders."

More information: R.N. Moda-Sava el al., "Sustained rescue of prefrontal circuit dysfunction by antidepressant-induced spine formation," *Science* (2019). science.sciencemag.org/cgi/doi … 1126/science.aat8078

"Do antidepressants restore lost synapses?" *Science* (2019). science.sciencemag.org/cgi/doi … 1126/science.aax0719

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