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Neurobiology

Could new synapses lift spirits?

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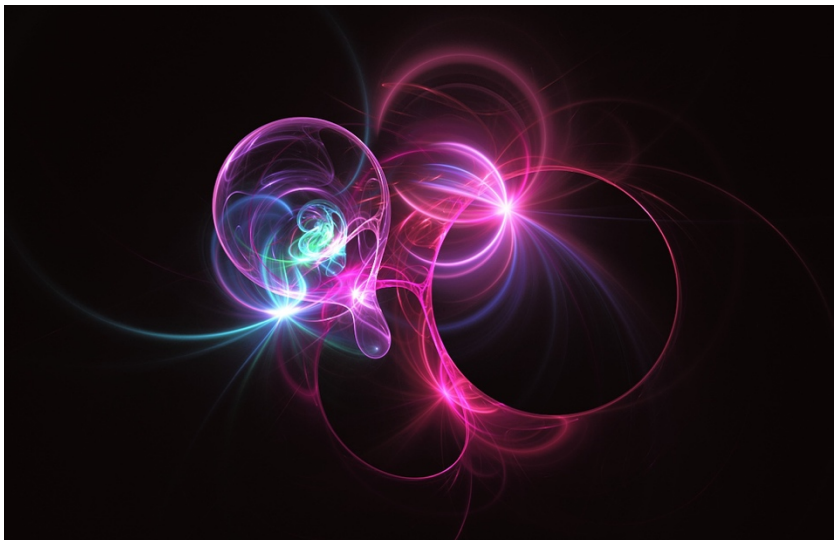
ABSTRACT

Depression is a leading concern for public health, however, the available treatments are insufficient for many patients. Ketamine is a promising yet enigmatic new antidepressant option. Recent work by Moda-Sava, Murdock, Parekh, and colleagues explores how ketamine remodels the connections between brain cells in mice.



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In her memoir *The Scar: A Personal History of Depression and Recovery*, author Mary Cregan reflects on a conversation with a psychiatrist, hours after an attempt on her own life: "Thinking of myself in this interview brings to mind an image: a miner, at the end of his shift, lies down in a wheeled wooden cart on iron tracks. In this way he is carried up through a tunnel from deep underground, back to the surface of the earth and to daylight, blinking and black with soot."

After a long battle, Cregan achieved a fragile relief from her severe illness. But for many of the roughly 300 million people worldwide living with depression, current treatments are tragically inadequate. Patients need to medicate for a long time to achieve positive effects and many never fully recover. Almost three decades ago, clinicians incidentally observed that the anesthetic, ketamine, could relieve depressive symptoms within hours. As one of the most exciting advances in psychiatry, ketamine could transform how we approach treatment-resistant depression. The American Food and Drug Administration has recently approved esketamine (a variant) for clinical use as an antidepressant. The promise of ketamine lies in the fact that it is an entirely new class of compound, targeting fast neurotransmission systems instead of the slower ones targeted conventionally. However, several questions remain about the neurobiological actions of this enigmatic new treatment. How does ketamine alter brain communication circuits to achieve rapid antidepressant effects? Does the same mechanism sustain ketamine's effect over time?

To begin to address these questions, we turned to a mouse model. While no animal model fully captures the nuances of a human psychiatric illness, scientists accept that exposing mice to stress recapitulates several aspects of depression-like behavior. To explore how stress affects the brain, we used two-photon microscopy, a technique that enables long-term imaging of brains in live animals. We specifically observed the medial prefrontal cortex, a region essential for higher order cognitive processes that malfunction in depression. To function, the brain needs to pass signals between neurons, the individual cells that comprise it. Neurons form close connections to communicate with one another - these connections are termed synapses. We repeatedly imaged small structures on the neurons called dendritic spines. These are tiny protrusions from neurons' branches that form synapses. We observed that chronic stress exposure eliminated many spines and synapses, but a single antidepressant dose of ketamine could reverse this effect. In fact, some of the newly formed spines appeared in the same location as those lost after stress. We then used an optical tool to selectively shrink and eliminate recently formed spines and found that this disrupted the long-term recovery from depression. That means that the new spines were responsible for the long-term antidepressant effect of ketamine.

We then wanted to investigate whether disappearing and reappearing spines affect communication between brain cells. Neurons are active when they are "firing" action potentials or electrical impulses. We performed calcium imaging to noninvasively monitor the activity of many neurons. When neurons are actively relaying signals, calcium enters their bodies and binds to a calcium indicator protein we introduced into the cells. This binding causes the protein to change shape and emit light that gets stronger with increasing neural activity. We found that chronic stress disrupted the normal synchronous action potential firing of medial prefrontal cortical neurons. After ketamine treatment, many of the connectivity patterns returned to pre-stress levels. Surprisingly, the activity patterns recovered before the new spines appeared. Our data suggest that, while spine formation sustains antidepressant effects long-term, it does not play a role in the initial response to ketamine.

Ketamine's antidepressant effects wear off after 1-2 weeks and its repeated use can lead to addiction. Uncovering how this compound works could help to develop improved next-generation antidepressants. Our results suggest that strategies enhancing spine survival may prolong the effect of ketamine. Surveying current treatment options, Mary Cregan contends that, "while we await a more thorough understanding of the processes that result in severe depression, and until the next treatment innovations arrive, these drugs – imperfect, uncomfortable, but life-saving nonetheless – are what we have."