MENTAL HEALTH

Getting the Inside Dope on Ketamine's Mysterious Ability to Rapidly Relieve Depression

The notorious party drug may act as an antidepressant by blocking neural bursts in a little-understood brain region that may drive depression

By Simon Makin on March 2, 2018

Credit: Voisin *Getty Images*

Ketamine has been called the biggest thing to happen to psychiatry in 50 years, due to its uniquely rapid and sustained antidepressant effects. It improves symptoms in as little as 30 minutes, compared with weeks or even months for existing antidepressants, and is effective even for the roughly one third of patients with so-called treatment-resistant depression.

Although there are multiple theories, researchers do not quite know how ketamine combats depression. Now, new research has uncovered a mechanism that may, in part, explain ketamine's antidepressant properties. Two studies recently published in *Nature* describe a distinctive pattern of neural activity that may drive depression in a region called the lateral habenula (LHb); ketamine, in turn, blocks this activity in depression-prone rats.

Originally licensed as an anesthetic in 1970, ketamine has since gained fame as a party drug for causing out-of-body experiences, hallucinations and other psychosislike effects. Its antidepressant properties in humans were discovered almost 20 years ago. Ketamine does not directly influence the same chemical messengers as standard antidepressants such as serotonin, but rather works via interaction with another chemical, glutamate—not usually associated with mood but rather with brain plasticity. One prominent idea about how it alleviates depression is by promoting the growth of new neural connections. “We provide a new angle for people to think about how this drug works,” says neuroscientist Hailan Hu of Zhejiang University in China, leader of the team that conducted both studies. If she is right, her group may have identified multiple new lines of attack for treating a condition the World Health Organization calls the leading cause of disability worldwide.

Both new studies probe the workings of the LHb, a small, central brain region that acts like the dark twin of the brain's reward centers by processing unexpectedly unpleasant events. For example, if an animal has been trained to expect food when reaching the end of a maze and the reward is not there, the activates, signaling a discrepancy between expectation and outcome. This has led to the LHb being dubbed the key part of a "disappointment circuit." If the LHb is overactive, it could suppress rewards from normally pleasurable activities—a symptom known as anhedonia—leading to long-term apathy and hopelessness. Studies in animals suggest hyperactivity in the LHb contributes to depression, but the details have been murky.

The first study, led by neuroscientist Yan Yang, also at Zhejiang, discovered a distinctive pattern of rapid bursts in the LHb of rats that display depressionlike behaviors. More usual neural activity, where neurons fire at spaced intervals, was not related to depression, suggesting it is burst activity, rather than increased LHb activity per se, that is related to depression. Exactly why bursts are important is not clear, but the researchers think they may enhance communication with other regions. "It's like a machine-gun shooting versus single shooting, so it carries information more efficiently to downstream brain areas," Hu says. The team also provoked LHb neurons into burst firing using optogenetics, a technology that allows neurons to be activated with light. The results showed increased depressive behaviors, indicating the bursts actually cause depression rather than just occur alongside it.

The researchers stumbled on ketamine after they injected a drug that blocks NMDA receptors (for glutamate that, when activated, allow calcium to flood inside cells, causing them to fire) in the LHbs of depression-prone rats and saw strong antidepressant effects. Ketamine also blocks NMDA receptors, so the team repeated this with ketamine and again alleviated depression, within one hour. "We show that infusion of ketamine into just one brain region is sufficient to cause rapid antidepressant effects," Hu says. Studies of brain tissue samples showed that whereas ketamine silenced burst firing within minutes, the

standard antidepressant fluoxetine hydrochloride, commonly known as Prozac, had no such effect at these timescales.

The second study, led by Zhejiang neuroscientist Yihui Cui, looked at what might cause burst firing in depression. The researchers found a protein, Kir4.1, was present at higher levels in depressive rats. Kir4.1 is found in cells called astrocytes, which influence neuronal activity. The team showed this protein promotes burst firing in LHb neurons. Raising Kir4.1 levels increased depressionlike behaviors whereas blocking its function reduced them.

The studies do not reveal how burst firing influences depression but the researchers have a hypothesis. The LHb connects to parts of the limbic system—which processes emotion—as well as reward centers that signal using chemical messengers associated with pleasure and mood, like dopamine and serotonin. The LHb inhibits activity in these regions, so burst firing may more effectively put the brakes on systems that produce reward signals from pleasurable activities. “Our results provide a simple model of how ketamine leads to disinhibition of the reward center to quickly relieve depression,” Hu says.

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Among researchers not taking part in the work, not everyone agrees the story can be this simple, however. “We’ve found the habenula is underactive in depressed patients, which is inconsistent with these data,” says neuroscientist Jonathan Roiser of University College London. But if these discrepancies can be resolved, studying the LHb is a promising path

toward entirely new approaches to treating severe depression. “It’s fascinating to see that ketamine dampens habenular hyperactivity,” says psychiatrist Matthew Klein of the University of California, San Diego. “Further research will show whether this is the rapid antidepressant mechanism in human patients.”

The new findings have several implications for treatment. Understanding how ketamine acts so quickly could provide greater insight into the core mechanisms of depression and help to develop next-generation ketamine-based treatments that do not have the same side effects as the drug itself, such as dissociation and bladder problems. Several pharmaceutical companies have been pursuing this goal, but knowing what it is about ketamine that produces the desirable effects could, in principle, aid these efforts.

Researchers are still studying ketamine’s long-term effects, safety and optimum doses in clinical trials. Currently, patients are administered ketamine via infusions in a hospital, which, combined with the side effects, makes it unwieldy. “It would be great if we could reproduce ketamine’s rapid effects in a simple oral medication,” Klein says. “Its most exciting benefit is in treating suicidal ideation, which we currently don’t have any fast-acting therapies for; it’s an unmet clinical need that could save lives.”

The recent work also identifies multiple new targets for therapies, including Kir4.1 and t-type voltage-sensitive calcium channels (t-VSCCs), another target implicated in burst firing. The team is planning to test whether drugs that block t-VSCCs have antidepressant effects, Hu says.

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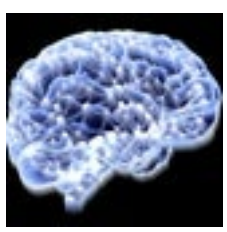

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