Ketamine's antidepressive effects tied to opioid system in brain, scientists say

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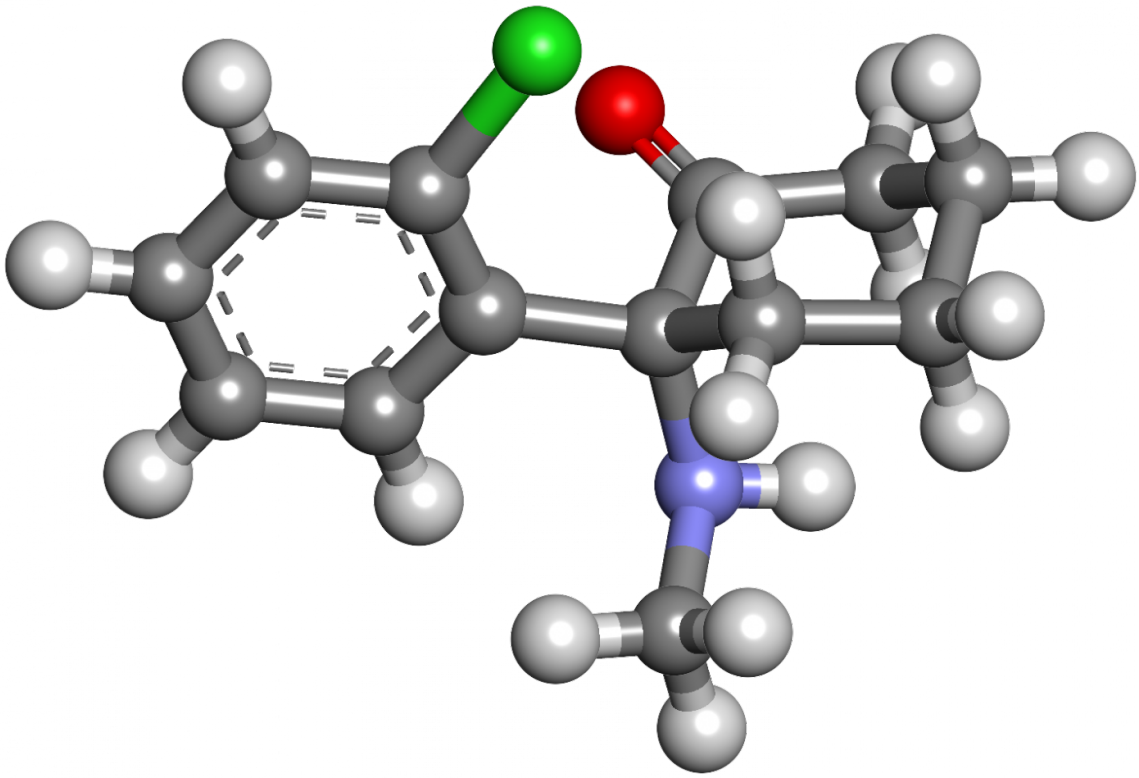

3D model of Ketamine. Credit: Wikipedia

Scientists at the Stanford University School of Medicine have discovered that ketamine works as an antidepressant at least in part by activating the

brain's opioid system.

The finding overturns previously held beliefs that the drug's antidepressant effects stemmed solely from its impact on the glutamate system. These beliefs led to the widespread use of ketamine to treat depression and spurred the development of glutamate-blocking drugs for use as antidepressants.

The new finding also highlights the interaction between depression, pain and opioid addiction and presents an opportunity for clinicians to reframe treatment approaches for three of the most important public health crises today.

The research is believed to be the first to address how ketamine works in the human brain to provide relief from depression. A paper describing the work will be published Aug. 29 in The *American Journal of Psychiatry*.

"Before we did the study, I wasn't sure that ketamine really worked to treat depression. Now I know the drug works, but it doesn't work like everyone thought it was working," said Alan Schatzberg, MD, the Kenneth T. Norris Jr. Professor of Psychiatry and Behavioral Sciences, who shares senior authorship of the paper with Carolyn Rodriguez, MD, Ph.D., assistant professor of psychiatry and behavioral sciences.

Ketamine's origins

Ketamine was developed in the 1960s and has been used for decades as an anesthetic during surgery. It can cause dissociative side effects, including hallucinations, and has been used as a recreational drug. If used regularly, it can lead to dependence.

Although the Food and Drug Administration has not approved the drug's

use for depression, some doctors have prescribed it "off-label" in recent years as a rapid but short-acting antidepressant. Traditional antidepressants, such as selective serotonin reuptake inhibitors, take four to six weeks to have an effect but don't work in two-thirds of patients who try them. Stand-alone ketamine clinics have popped up all over the country to administer expensive intravenous infusions of ketamine to patients, even though some scientists caution that not enough is known about the drug to warrant its widespread use for depression.

Ketamine infusions are also used to treat chronic pain, which is a common condition in depressed patients. Exactly how ketamine blunts pain is not fully understood, but it is known to work at least in part on the opioid system. The Stanford researchers wanted to see if the antidepressive effects of ketamine were also generated by ketamine's activation of the opioid system. They sought to answer this question through a small clinical trial in which people with depression were given an opioid-receptor blocker prior to taking ketamine.

The study enrolled adults with treatment-resistant depression, meaning their condition had not improved after multiple treatment efforts. Twelve participants received infusions of ketamine twice—once preceded by naltrexone, an opioid-receptor blocker, and once with placebo. Neither the study participants nor the researchers were told whether active drug or placebo was administered during each test. The researchers found that ketamine reduced depressive symptoms by about 90 percent for three days in more than half of the participants when administered with a placebo, but had virtually no effect on depressive symptoms when it was preceded by naltrexone.

"This was purely a mechanistic study, not a treatment trial," said Nolan Williams, MD, clinical assistant professor of psychiatry and behavioral science. "And the results were so clear that we ended the study early to avoid exposing additional patients to the ineffective combination

treatment." Williams shares lead authorship of the paper with Boris Heifets, MD, Ph.D., clinical assistant professor of anesthesiology, perioperative and pain medicine.

Because the field of anesthesia has long regarded ketamine specifically as a nonopioid drug, Heifets was skeptical when Williams approached him about joining the research effort. "Everything that I was taught, and everything that I've always taught my students—all of the evidence supports the fact that ketamine is not an opioid," he said. "I was really surprised at the results."

Understanding how it works

Although some small studies have shown that ketamine had rapid, although transient, antidepressant effects, Schatzberg said the researchers wanted to understand how ketamine works. He said he came to suspect that ketamine's effects might be linked to the brain's opioid system when Rodriguez published a report on ketamine's ability to reduce symptoms of obsessive compulsive disorder, which was similar to previous Stanford research using the opioid morphine.

The prevailing hypothesis for ketamine's antidepressant effect was that the drug blocked a receptor for glutamate, an excitatory neurotransmitter in the brain that is implicated in memory and learning. "But ketamine's mechanism is complicated, as it acts on many different receptor types beyond glutamate receptors, and it acts in three distinct phases—rapid effects, sustained effects and return to baseline," Rodriguez said.

Schatzberg noted that no other glutamate-receptor blocker has an antidepressant effect like ketamine and that attempts to develop similar drugs have largely failed.

The researchers said the findings from the new study may explain why

ketamine works so quickly as an antidepressant: It activates the brain's opioid receptors during its first phase of activity. The glutamate system may be responsible for the sustaining effects after ketamine is metabolized, they said.

The authors say that revealing the role of the opioid system in the antidepressant effects of ketamine is critical in the effort to develop new antidepressants. For instance, glutamate receptor blockers may not have rapid antidepressant effects unless they also involve the opioid system, Williams said.

"Psychiatry used opioids, barbiturates and high doses of stimulants to treat depression 50 or 60 years ago," Schatzberg said. "We have to properly examine the risks associated with using drugs of abuse—even in low doses—to treat depression. It's not limited to ketamine; other antidepressant drugs that target the opioid system are in development now, too."

While a standard opioid like morphine initially has an antidepressant effect, it promotes depression after repeated use, Williams said. People who are depressed take as much as 2.4 times as many opioids immediately after painful surgeries than those who aren't depressed, he said. "There is truly a link between depression, pain and opioid use," Heifets said. "You can't go after one without addressing the others."

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