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Is ketamine a panacea for depression?

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Researchers have long been intrigued by the antidepressant qualities of the club drug ketamine. Known on the street as "Special K," the drug is taken by partiers for its brief dissociative hallucinogenic effect, but it is also used medically as an anesthetic. It can banish severe depression for weeks at a time, but designer drugs that can mimic ketamine's effects on depression—without its hallucinogenic side effects—have proved difficult to develop.

Researchers led by Mark Rasenick, distinguished professor of physiology and biophysics and psychiatry in the University of Illinois at Chicago College of Medicine, have uncovered a previously unknown mechanism by which ketamine may relieve depression. Rasenick will present his findings May 20 at the meeting of the Society of Biological Psychiatry in San Diego.

"We wanted to determine what are the molecular events responsible for the rapid antidepressant effect of ketamine so that we can design a drug that does the same thing but without the side effects," Rasenick said.

In previous research, Rasenick and colleagues showed that SSRIs—the most commonly prescribed class of antidepressants, which includes Prozac and Zoloft—work in the brain by moving molecules called G proteins off of "lipid rafts" on the cell membrane where the G proteins are held inactive. G proteins produce cyclic AMP, which nerve cells need to signal properly. People with depression, Rasenick found, tend to have high levels of G proteins packed into these membrane patches, along with dampened nerve cell signaling, which may contribute to

symptoms of depression, including a feeling of overall numbness.

In the earlier research, when Rasenick exposed rat nerve cells to SSRIs, the drug accumulated in the lipid rafts, and G proteins moved out of the rafts. The movement was gradual, over the span of several days, which Rasenick thinks is the reason why SSRIs and most other antidepressants can take a long time to begin working.

In his current research, Rasenick and his colleagues performed a similar experiment with ketamine and noticed that the G proteins left the rafts much faster. G proteins began migrating out of the lipid rafts within 15 minutes.

The finding contradicts the long-held idea that ketamine works solely by blocking the NDMA receptor, which sits on the surface of nerve cells and helps transmit signals. Other drugs that block NDMA receptors don't have any effect on G protein levels in lipid rafts, suggesting that ketamine has another site of action in addition to blocking NDMA.

"Our finding holds promise for the development of new treatments for depression, especially for people who have not responded to currently available drugs," Rasenick said.

Ketamine and related compounds are also known to impact levels of glutamate, while most antidepressant drugs work on serotonin, norepinephrine or dopamine. Some studies have shown that malfunctions in the metabolism of glutamate may play a role in depression.

Provided by University of Illinois at Chicago