Researchers describe secrets of 'magic' antidepressant

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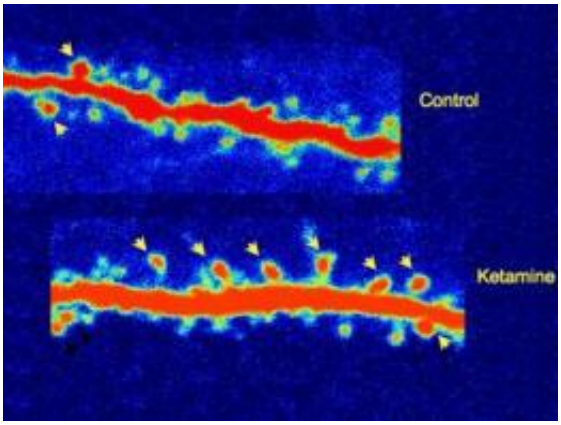

The bottom slide shows regeneration of synaptic connections in group receiving ketamine, compared to control group. Credit: Courtesy of Yale University

Yale researchers have discovered how a novel anti-depressant can take effect in hours, rather than the weeks or months usually required for most drugs currently on the market. The findings, described in the August 20 issue of the journal *Science*, should speed development of a safe and easy-to-administer form of the anti-depressant ketamine, which has already proven remarkably effective in treating severely depressed patients.

The Yale scientists found that, in rats, ketamine not only quickly improves depression-like behaviors but actually restores connections between brain cells damaged by chronic stress.

"It's like a magic drug -- one dose can work rapidly and last for seven to 10 days," said Ronald Duman, professor of psychiatry and pharmacology at Yale and senior author of the study.

Ketamine traditionally has been used as a general anesthetic for children, but a decade ago researchers at the Connecticut Mental Health Center found that, in lower doses, the drug seemed to give patients relief from depression, Duman said. In these initial clinical studies, which have been replicated at the National Institute of Mental Health, almost 70 percent of patients who are resistant to treatment with all other forms of antidepressants were found to improve within hours after receiving ketamine. However, its clinical use has been limited because it has to be delivered intravenously under medical supervision and in some cases can cause short-term psychotic symptoms. It has also been used as a recreational drug, known as "Special K" or sometimes just "K."

So Duman, colleague George Aghajanian and the Yale team set out to map the molecular action of the drug in the prefrontal cortex of rats that could lead to potential targets for a safer and more easily used drugs. The team discovered that ketamine acts on a pathway that rapidly forms new synaptic connections between neurons—a process called "synaptogenesis."

"The pathway is the story. Understanding the mechanism underlying the antidepressant effect of ketamine will allow us to attack the problem at a variety of possible sites within that pathway," Aghajanian said.

The team identified a critical point in the pathway, the enzyme mTOR, which controls protein synthesis required for new synaptic connections. There are already promising leads on ways to sustain the initial rapid effect of ketamine by intervening at specific downstream targets.

An estimated 40 percent of people suffering depression do not respond

to medication. And many others only respond after many months or years of trying different treatments. The authors note that ketamine also has been tested as a means to rapidly treat people with suicidal thoughts, a benefit usually not seen until weeks of treatment with traditional antidepressants.

Provided by Yale University