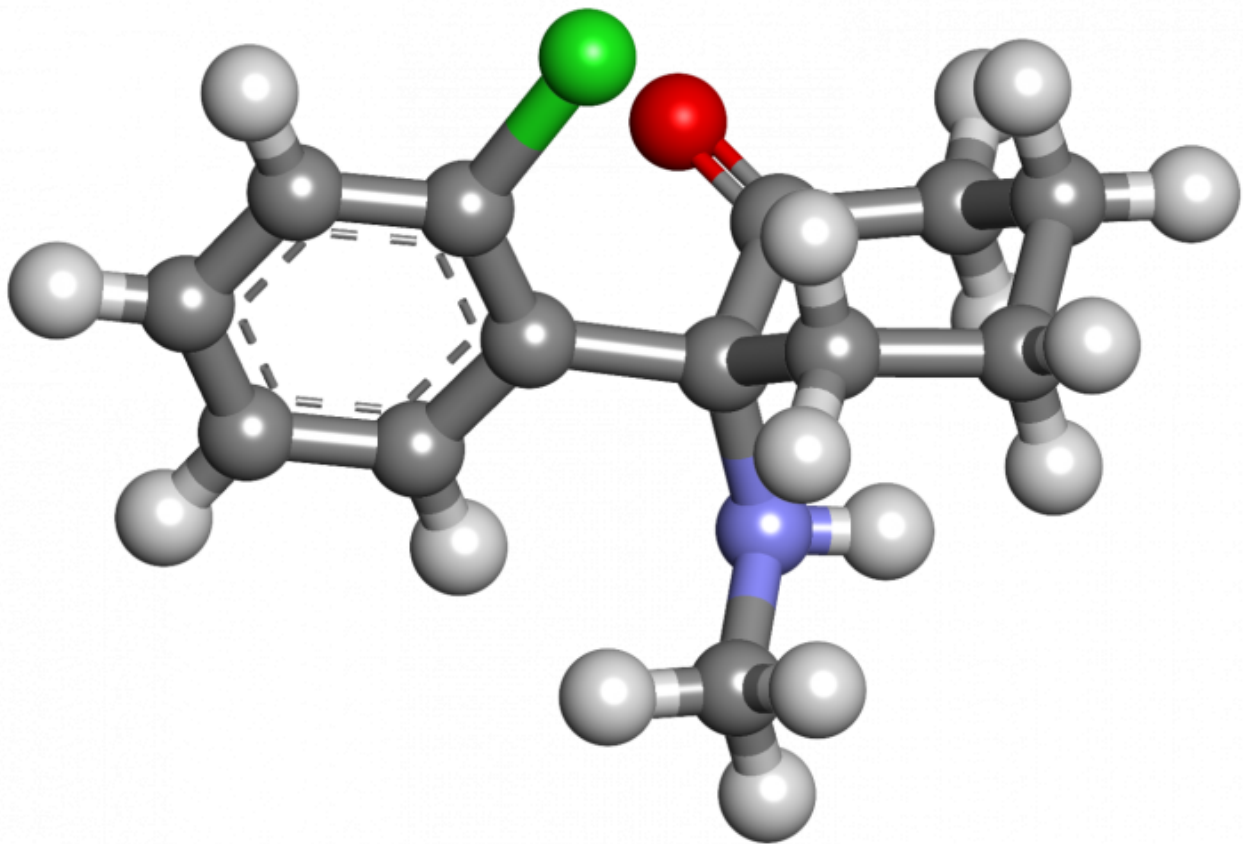


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Why ketamine is a speedster antidepressant

by Northwestern University



3-D model of Ketamine. Credit: Wikipedia

Ketamine is the speedster of antidepressants, working within hours compared to more common antidepressants that can take several weeks. But ketamine can only be given for a limited amount of time because of its many side effects.

Now, a new Northwestern Medicine study identifies for the first time exactly how [ketamine](#) works so quickly, and how it might be adapted for use as a drug without the [side effects](#).

The study in mice shows ketamine works as a rapid antidepressant by increasing the activity of the very small number of newborn neurons, which are part of an ongoing neurogenesis in the brain.

New neurons are always being made at a slow rate. It's been known that increasing the number of neurons leads to [behavioral changes](#). Other [antidepressants](#) work by increasing the rate of neurogenesis, in other words, increasing the number of neurons. But this takes weeks to happen.

By contrast, ketamine produces behavioral changes simply by increasing the activity of the existing [new neurons](#). This can happen immediately when the cells are activated by ketamine.

"We narrowed down the population of cells to a small window that is involved," said lead study author Dr. John Kessler, a professor of neurology at Northwestern University Feinberg School of Medicine and the Ken and Ruth Davee Professor of Stem Cell Biology. "That's important because when you give ketamine to patients now, it affects multiple regions of the brain and causes a lot of adverse side effects. But since we now know exactly which cells we want to target, we can design drugs to focus only on those cells."

The side effects of ketamine include blurred or [double vision](#), nausea, vomiting, insomnia, drowsiness and addiction.

The study was published recently in *Nature Communications*.

Goal to develop faster-working antidepressant

"The goal is to develop an antidepressant that doesn't take three to four weeks to work because people don't do well during that period of time," Kessler said. "If you are badly depressed and start taking your drug and nothing is happening, that is depressing in itself. To have something that works right away would make a huge difference."

Newborn neurons act like a match to ignite activity in neurons

"We prove [neurogenesis](#) is responsible for the behavioral effects of ketamine," Kessler said. "The reason is these newborn neurons form synapses (connections) that activate the other cells in the hippocampus. This small population of cells acts like a match, starting a fire that ignites a bunch of activity in a lot of other cells that produce the behavioral effects."

"However, it has not been understood that the same behavioral changes can be accomplished by increasing the activity of the new neurons without increasing the rate at which they are born," Kessler said. "This obviously is a much more rapid effect."

For the study, Northwestern scientists created a mouse in which only the very small population of newborn neurons had a receptor that allowed these cells to be silenced or activated by a drug that

did not affect any other cells in the brain. Scientists showed if they silenced the activity of these cells, ketamine didn't work anymore. But if they used the drug to activate this population of cells, the results mirrored those of ketamine. This showed conclusively that it is the activity of these [cells](#) that is responsible for the effects of ketamine, Kessler said.

More information: Radhika Rawat et al, Ketamine activates adult-born immature granule neurons to rapidly alleviate depression-like behaviors in mice, *Nature Communications* (2022). DOI: [10.1038/s41467-022-30386-5](https://doi.org/10.1038/s41467-022-30386-5)

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