Faster-acting antidepressants closer to becoming a reality

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A new study has revealed more about how the medication ketamine, when used experimentally for depression, relieves symptoms of the disorder in hours instead of the weeks or months it takes for current antidepressants to work. While ketamine itself probably won't come into use as an antidepressant because of its side effects, the new finding moves scientists considerably closer to understanding how to develop faster-acting antidepressant medications – among the priorities of the National Institute of Mental Health (NIMH), part of the National Institutes of Health.

Ketamine blocks a receptor called NMDA on brain cells, an earlier NIMH study in humans had shown, but the new study in mice shows that this is an intermediate step. It turns out that blocking NMDA increases the activity of another receptor, AMPA, and that this boost in AMPA is crucial for ketamine's rapid antidepressant actions. The study was reported online in *Biological Psychiatry* on July 23, by NIMH researchers Husseini K. Manji, MD, Guang Chen, MD, PhD, Carlos Zarate, MD, and colleagues.

"Our research is showing us how to develop medications that get at the biological roots of depression. This new finding is a major step toward learning how to improve treatment for the millions of Americans with this debilitating disorder; toward eliminating the weeks of suffering and uncertainty they have to endure while they wait for their medications to work," said NIH Director Elias Zerhouni, M.D.

Almost 15 million American adults have a depressive disorder. During the long wait to begin feeling the effects of conventional medications, patients may worsen, raising the risk of suicide for some. Depressive disorders also affect children and adolescents.

By aiming new medications at more direct molecular targets, such as NMDA or AMPA, scientists may be able to bypass some of the steps through which current antidepressants indirectly exert their effects – a roundabout route that accounts for the long time it takes for patients to begin feeling better with the conventional medications.

While ketamine appears to achieve this, it is an unlikely candidate to become a new treatment for depression, because of the side effects it can cause in humans, including hallucinations. It is approved as an anesthetic by the Food and Drug Administration at much higher doses than those given in the study, but its use is limited because it may cause hallucinations during recovery from anesthesia.

Both NMDA and AMPA are receptors for the neurotransmitter glutamate, one of the chemical messengers that enable brain cells to communicate with each other. The glutamate system has been implicated in depression recently, leading to efforts to unravel its molecular machinery in search of abnormalities and of better targets for antidepressant medications.

This focus on the glutamate system is a departure from the thinking that led to currently available antidepressants, which are thought to relieve depression through a lengthy trickle-down process of biochemical reactions that affect the circuitry underlying depression.

The fact that NMDA and AMPA receptors are part of the glutamate system and that targeting them directly led to such rapid, sustained relief of depression-like behaviors in this study – and that a single dose of

ketamine did the same in humans in the earlier study – suggests that they are probably the key targets for antidepressant medications.

“In any other illness of depression’s magnitude, patients aren’t expected to just accept that their treatments won’t start helping them for weeks or months. The value of our research on compounds like ketamine is that it tells us where to look for more precise targets for new kinds of medications that can close the gap,” said NIMH Director Thomas R. Insel, MD. “We’re making tremendous progress.”

To conduct the new study, researchers induced depression-like behaviors in mice; for example, the mice gave up after being forced to engage in hopeless tasks, such as prolonged swimming. A dose of ketamine reversed the depression-like behaviors for at least two weeks.

When the researchers gave the mice a substance that blocks the AMPA receptor beforehand, ketamine was not able to reverse the depression-like behaviors. The boost in AMPA thus appears to be a necessary ingredient for ketamine’s antidepressant effects.

In a related experiment, the scientists used two different compounds instead of ketamine to try to block just one part of the NMDA receptor, an even more precise target. These other compounds also reduced depressive behaviors, suggesting that it may be feasible to develop other fast-acting antidepressants without ketamine’s side effects.

“Today’s antidepressant medications eventually end up doing the same thing, but they go about it the long way around, with a lot of biochemical steps that take time. Now we’ve shown what the key targets are and that we can get at them rapidly,” said Zarate. “Ketamine probably can’t become the medication of choice, but this research is leading to some very real possibilities for a whole new generation of antidepressant medications.”

Source: National Institute of Mental Health