

Researchers explore the antidepressant effects of ketamine

Drug treatments for depression can take many weeks for the beneficial effects to emerge. The excruciating and disabling nature of depression highlights the urgency of developing treatments that act more rapidly. Ketamine, a drug used in general medicine as an anesthetic, has recently been shown to produce improvements in depressed patients within hours of administration. A new study being published in the February 15th issue of *Biological Psychiatry* provides some new insight into the mechanisms by which ketamine exerts its effects.

Ketamine is classified as an N-methyl d-aspartate (NMDA) glutamate receptor antagonist. Maeng and colleagues now provide new evidence that these antidepressant effects of NMDA receptor antagonists are mediated by their ability to increase the stimulation of α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) glutamate receptors.

In other words, their findings indicate that the antidepressant-like effects of drugs like ketamine are dependent on AMPA receptor stimulation. This suggests that drugs that enhance AMPA receptor function might have rapid antidepressant properties.

Dr. Hussein Manji, corresponding author on this paper and a Deputy Editor of *Biological Psychiatry*, explains that “by aiming new medications at more direct molecular targets, such as NMDA or AMPA, we 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.” He adds, “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.”

This study is especially important because even though this important antidepressant effect has been found in ketamine, its use also has significant drawbacks. According to John H. Krystal, M.D., Editor of *Biological Psychiatry* and affiliated with both Yale University School of Medicine and the VA Connecticut Healthcare System, “the only NMDA receptor antagonist found to be effective so far, ketamine, produces transient changes in perception and impairments in cognition.”

It is also in the same class of drugs as PCP (phencyclidine) and can cause hallucinations, among other side effects. Dr. Krystal notes that “it is possible that drugs that directly enhance the activity of AMPA glutamate receptors, the AMPAkinetics, would have antidepressant effects similar to ketamine, without the unwanted side effects.” Exploring the antidepressant effects of the AMPAkinetics will now be an important target for researchers.

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