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Would an 'anti-ketamine' also treat depression?

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Thirteen years ago, an article in this journal first reported that the anesthetic medication, ketamine, showed evidence of producing rapid antidepressant effects in depressed patients who had not responded to prior treatments. Ketamine works by blocking one of the targets for the neurotransmitter glutamate in the brain, the N-methyl-D-aspartate (NMDA) glutamate receptor.

Now, a new study in *Biological Psychiatry* reports that enhancing, instead of blocking, that same target – the NMDA glutamate receptor – also causes antidepressant-like effects.

Scientists theorize that NMDA receptor activity plays an important role in the pathophysiology of depression, and that normalizing its functioning can, potentially, restore mood to normal levels.

Prior studies have already shown that the underlying biology is quite complex, indicating that both hyperfunction and hypofunction of the NMDA receptor is somehow involved. But, most studies have focused on antagonizing, or blocking, the receptor, and until now, studies investigating NMDA enhancement have been in the early phases.

Sarcosine is one such compound that acts by enhancing NMDA function. Collaborators from China Medical University Hospital in Taiwan and the University of California in Los Angeles studied sarcosine in an animal model of depression and, separately, in a clinical trial of depressed patients.

"We found that enhancing NMDA function can improve depression-like behaviors in rodent models and in human depression," said Dr. Hsien-Yuan Lane, the corresponding author on the article.

In the clinical portion of the study, they conducted a 6-week trial where 40 depressed patients were randomly assigned to receive sarcosine or citalopram (Celexa), an antidepressant already on the market that was used as a comparison drug. Neither the patients nor their doctors knew which one they were receiving.

Compared to citalopram, patients receiving sarcosine reported significantly improved mood scores, were more likely to experience relief of their depression symptoms, and were more likely to continue in the study. There were no major side effects in either group, but patients receiving citalopram reported more relatively minor side effects than the patients being treated with sarcosine.

"It will be important to understand how sarcosine, which enhances NMDA receptor function, produces the interesting effects reported in this study. There are ways that its effects, paradoxically, might converge with those of ketamine, a drug that blocks NMDA receptors," commented Dr. John Krystal, Editor of *Biological Psychiatry*. "For example, both compounds may enhance neuroplasticity, the capacity to remodel brain networks through experience. Also, both potentially attenuate signaling through NMDA receptors, ketamine with single doses and sarcosine, with long-term administration, by evoking an adaptive down regulation of NMDA receptors."

Better understanding the reported findings may help to advance the development of medication treatments for patients who do not respond to available treatments. This is an important goal, with estimates indicating that as many as half of all patients do not experience complete relief of their depression.

More information: The article is "Inhibition of Glycine Transporter-I as a Novel Mechanism for the Treatment of Depression" by Chih-Chia Huang, I-Hua Wei, Chieh-Liang Huang, Kuang-Ti Chen, Mang-Hung Tsai, Priscilla Tsai, Rene Tun, Kuo-Hao Huang, Yue-Cune Chang, Hsien-Yuan Lane, and Guochuan Emil Tsai (DOI: 10.1016/j.biopsych.2013.02.020). The article appears in *Biological Psychiatry*, Volume 74, Issue 10 (November 15, 2013)

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