

Research shows why ketamine is an effective antidepressant but memantine is not

May 27 2014, by Marcia Malory



One 10 ml vial of 1000 mg ketamine. Credit: Psychonaught/Wikipedia

(Medical Xpress)—Ketamine is a fast-acting antidepressant. However, it

can create symptoms that mimic psychosis. Therefore, doctors don't give it to depressed patients. Memantine, a similar drug, does not have psychotomimetic effects, but it also does not appear to alleviate depression. Lisa M. Monteggia of the University of Texas Southwestern Medical Center and her colleagues have determined that these drugs have different effects on neurotransmitter pathways. In particular, ketamine promotes the expression of neurotrophic factors but memantine doesn't. The research appears in the *Proceedings of the National Academy of Sciences*.

Traditional antidepressants target the monoamine system. Patients who take them require several weeks of treatment before they begin to feel an effect. In some cases, for example, if the patient is suicidal, waiting this long can be dangerous. A fast-acting antidepressant would be a preferable treatment.

Ketamine is such a fast-acting drug. Patients have reported experiencing its antidepressant effects within 30 minutes to a few hours after a single intravenous dose. Unlike traditional antidepressants, [ketamine](#) does not affect the monoamine system. It is an NMDA receptor antagonist. Unfortunately, it can cause [psychotic symptoms](#); therefore, doctors do not prescribe it for treatment of depression.

As an alternative to ketamine, pharmacologists have considered using the drug memantine, another NMDA receptor antagonist. Memantine, used to treat patients with Alzheimer's disease, does not cause psychotic symptoms and therefore would be safer to use. Clinical studies, however, have shown that it does not behave as an antidepressant. Until now, researchers haven't understood why.

To understand the differences between these two drugs, Monteggia's team first tested their antidepressant properties on mice. Tests confirmed previous observations that ketamine acts as an antidepressant

but memantine does not.

The team then used electrophysiology to examine the effect of ketamine and memantine on cultured mouse hippocampal neurons. They found key functional differences in how the drugs suppress NMDA receptor function at rest and how they inhibit the eukaryotic elongation factor 2 kinase (eEF2K) signaling pathway.

When the extracellular recording solution did not contain magnesium, both ketamine and memantine antagonized NMDA receptors. However, with the addition of magnesium, ketamine blocked NMDA receptors, but [memantine](#) did not. In addition, ketamine inhibited the phosphorylation of eEF2 and augmented expression of brain derived neurotrophic factor (BDNF). Memantine did not produce these effects. Augmentation of BDNF makes ketamine an effective antidepressant.

These findings could help scientists develop new, fast-acting antidepressants with fewer side effects.

More information: Mechanisms underlying differential effectiveness of memantine and ketamine in rapid antidepressant responses, *PNAS*, 2014. www.pnas.org/cgi/doi/10.1073/pnas.1323920111

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