Research shows why ketamine is an effective antidepressant but memantine is not
27 May 2014, by Marcia Malory

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 BNDF makes ketamine an effective antidepressant.

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


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