Ketamine helps see how the brain works in clinical depression

16 June 2011, by Deborah Braconnier

(Medical Xpress) -- In a new study published in *Nature*, Lisa Monteggia from the University of Texas Southwestern Medical Center looks at how the drug ketamine, typically used as an anesthetic or a popular recreational drug for its hallucinogenic affect, works in the brain to treat severe clinical depression.

Traditional antidepressants can take weeks or months before taking affect in treating depression and it is this critical time that finds many depressed patients committing suicide. Researchers have been looking for years to develop a drug that works to treat depression much quicker. According to this new study, mice receiving a ketamine injection showed fewer signs of depression within only a half an hour and the results lasted for as long as a week.

Monteggia and her team wanted to find out just how the ketamine was able to work so quickly and, by measuring changes in the brain, they discovered that ketamine increased the synthesis of BDNF, or brain-derived neurotrophic factor. This BDNF is a nerve growth factor that helps brain cells grow and develop new neurons.

Looking even further at what happens, they discovered that the increase in BDNF is caused by the ketamine deactivating a chemical called eEF2 kinase which normally suppresses BDNF production. This discovery and the connection of eEF2 to BDNF could potentially open the door to new drugs being created that target and block eEF2.

The possible development of drugs designed to block this eEF2 and allow for an increase in BDNF production could allow for much quicker results than seen in current antidepressants without the possible hallucinogenic side effects ketamine can cause.

While ketamine works in those with severe depression, it is not readily used on patients as psychiatrists are not familiar with the drug and are uncomfortable with its possible side effects.

More information: NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses, *Nature* (2011) doi:10.1038/nature10130

Abstract
Clinical studies consistently demonstrate that a single sub-psychomimetic dose of ketamine, an ionotropic glutamatergic NMDAR (N-methyl-D-aspartate receptor) antagonist, produces fast-acting antidepressant responses in patients suffering from major depressive disorder, although the underlying mechanism is unclear. Depressed patients report the alleviation of major depressive disorder symptoms within two hours of a single, low-dose intravenous infusion of ketamine, with effects lasting up to two weeks, unlike traditional antidepressants (serotonin re-uptake inhibitors), which take weeks to reach efficacy. This delay is a major drawback to current therapies for major depressive disorder and faster-acting antidepressants are needed, particularly for suicide-risk patients3. The ability of ketamine to produce rapidly acting, long-lasting antidepressant responses in depressed patients provides a unique opportunity to investigate underlying cellular mechanisms. Here we show that ketamine and other NMDAR antagonists produce fast-acting behavioural antidepressant-like effects in mouse models, and that these effects depend on the rapid synthesis of brain-derived neurotrophic factor. We find that the ketamine-mediated blockade of NMDAR at rest deactivates eukaryotic elongation factor 2 (eEF2) kinase (also called CaMKIII), resulting in reduced eEF2 phosphorylation and de-suppression of translation of brain-derived neurotrophic factor. Furthermore, we find that inhibitors of eEF2 kinase induce fast-acting behavioural antidepressant-like effects. Our findings indicate that the regulation of protein synthesis by spontaneous neurotransmission may

serve as a viable therapeutic target for the development of fast-acting antidepressants.