Brain signal ID's responders to fast-acting antidepressant

August 6 2012

(Medical Xpress) -- Scientists have discovered a biological marker that may help to identify which depressed patients will respond to an experimental, rapid-acting antidepressant. The brain signal, detectable by noninvasive imaging, also holds clues to the agent's underlying mechanism, which are vital for drug development, say National Institutes of Health researchers.

The signal is among the latest of several such markers, including factors detectable in blood, genetic markers, and a sleep-specific brain wave, recently uncovered by the NIH team and grantee collaborators. They illuminate the workings of the agent, called ketamine, and may hold promise for more personalized treatment.

"These clues help focus the search for the molecular targets of a future generation of medications that will lift depression within hours instead of weeks," explained Carlos Zarate, M.D., of the NIH's National Institute of Mental Health (NIMH). "The more precisely we understand how this mechanism works, the more narrowly treatment can be targeted to achieve rapid antidepressant effects and avoid undesirable side effects."

Zarate, Brian Cornwell, Ph.D., and NIMH colleagues report on their brain imaging study online in the journal Biological Psychiatry.

Dr. Zarate views subject in MEG scanner from scanner control room.

Previous research had shown that ketamine can lift symptoms of depression within hours in many patients. But side effects hamper its use as a first-line medication. So researchers are studying its mechanism of action in hopes of developing a safer agent that works similarly.

Ketamine works through a different brain chemical system than conventional antidepressants. It initially blocks a protein on brain neurons, called the NMDA receptor, to which the chemical messenger glutamate binds. However, it is not known if the drug's rapid antidepressant effects are a direct result of this blockage or of downstream effects triggered by the blockage, as suggested by animal studies.

To tease apart ketamine's workings, the NIMH team imaged depressed patients' brain electrical activity with magnetoencephalography (MEG). They monitored spontaneous activity while subjects were at rest, and activity evoked by gentle stimulation of a finger, before and 6.5 hours after an infusion of ketamine.

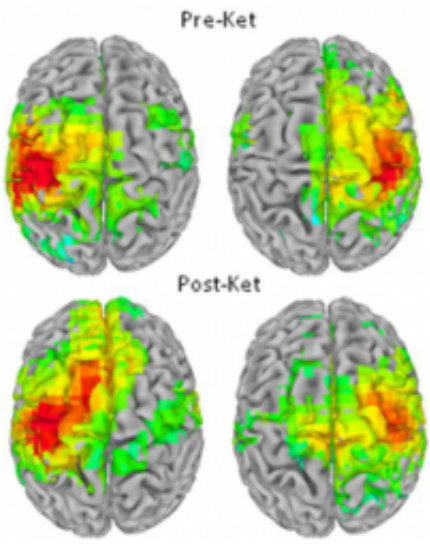
Images show response to finger stroking pre- and post-ketamine

obtained by MEG scanning.

It was known that by blocking NMDA receptors, ketamine causes an increase in spontaneous electrical signals, or waves, in a particular frequency range in the brain's cortex, or outer mantle. Hours after ketamine administration — in the timeframe in which ketamine relieves depression — spontaneous electrical activity in people at rest was the same whether or not the drug lifted their depression.

Electrical activity evoked by stimulating a finger, however, was different in the two groups. MEG imaging made it possible to monitor excitability of the somatosensory cortex, the part of the cortex that registers sensory stimulation. Those who responded to ketamine showed an increased response to the finger stimulation, a greater excitability of the neurons in this part of the cortex.

Such a change in excitability is likely to result, not from the immediate effects of blocking the receptor, but from other processes downstream, in the cascade of effects set in motion by NMDA blockade, say the researchers. Evidence points to changes in another type of glutamate receptor, the AMPA receptor, raising questions about whether the blocking of NMDA receptors is even necessary for ketamine's antidepressant effect. If NMDA blockade is just a trigger, then targeting AMPA receptors may prove a more direct way to effect a lifting of depression.



Images show response to finger stroking pre- and post-ketamine obtained by MEG scanning.

A separate study of ketamine biomarkers by the NIMH group adds to evidence that the drug may work, in part, by strengthening neural connections. Thirty treatment resistant depressed patients who received ketamine showed increased sleep-specific slow brainwave activity (SWA) — a marker of such strengthened synapses and of increased synchronization of networks in the cortex. They also had higher blood levels of a key neural growth chemical, brain-derived neurotrophic factor (BDNF), previously linked, in animal studies, to ketamine's action. Intriguingly, the boosts in BDNF were proportional to those in SWA only among 13 participants whose depressions significantly lifted – suggesting a potential marker of successful treatment.

"Linked SWA and BDNF may represent correlates of mood improvement following ketamine treatment," said Zarate. "These may be part of the mechanism underlying the rapid antidepressant effects and prove useful in testing potential new therapies that target the glutamate system."

The increases in SWA, detected via electroencephalography (EEG), were also reflected in increased slope and amplitude of individual brainwaves — additional indicators of neural health and adaptability.

Prior to discovery of ketamine's antidepressant effects, the only fast-acting antidepressant therapies were sleep deprivation and electroconvulsive therapy (ECT), both of which are also thought to work, at least in part, by stimulating BDNF.

There is also new evidence that people with one of two common versions of the gene that codes for BDNF respond better to ketamine — and clues about why. The versions are created by a site in the human BDNF gene where the genetic code differs slightly across individuals. Each person inherits two copies of the gene, one from each parent. So people can inherit one or two copies of each version.

In June, NIMH-funded researchers reported that ketamine's ability to spur the growth of neural connections and trigger antidepressant-like behavioral responses was impaired in mice genetically engineered to express two copies of a risk version of the human BDNF gene that is carried by about 30 percent of the population. NIMH grantees George Aghajanian M.D., and Ronald Duman, Ph.D., of Yale University, New Haven, Conn., also discovered atrophy in extensions of neurons and dampened electrical activity in key cells at the front of the brain, with the risk version.

The mouse results suggested that the same site of variability in the BDNF gene might similarly influence patients' responses to ketamine. In July, Zarate and NIMH colleagues reported that in 62 depressed patients, this variability in the BDNF gene accounted for 28 percent of difference in patients' responsiveness to the medication. As expected, the antidepressant effect was strongest in patients with two copies of the other, protective version, which is carried by about 60 percent of the

population.

These results strengthen the case for BDNF's pivotal role in mediating antidepressant effects produced via the glutamate system. They also suggest that it might be possible to improve ketamine's antidepressant effect in risk version carriers by first giving them treatments known to enhance BDNF, such as exercise, transcranial magnetic stimulation, ECT, or conventional antidepressants.

In another recent study by the NIMH team and NIH collaborators, by-products of the chemical breakdown of ketamine, detectable in blood, helped to sort out responders from non-responders, as well as diagnosis and symptoms. This first study of its kind pinpointed correlates of such downstream ketamine metabolites in 45 treatment resistant depressed unipolar and 22 depressed bipolar patients.

Blood levels of one metabolite were higher among bipolar non-responders, indicating that these patients might require a lower dose of the drug for optimal efficacy. Levels of three related metabolites were higher in bipolar patients, with only one, of a different type, elevated in patients with major depression. Higher levels of three metabolites of the former type were also associated with lower scores on measures of psychotic and other side effects, following ketamine treatment. The identification of these downstream metabolites opens the door to possibly developing them into newer treatments that are better tolerated than ketamine.

Ketamine also recently produced the fastest, strongest and longest-lasting anti-suicidal intervention ever demonstrated in a controlled trial, according to Zarate and colleagues. In a replication of an earlier study, the researchers confirmed that ketamine not only lifts depression, but also reduces suicidal thoughts in bipolar patients. The effects were detectable as soon as 40 minutes after a single infusion in 15 treatment

resistant patients taking mood stabilizers, and remained significant for at least a few days. Three fourths of the patients responded to ketamine, with none responding to a placebo. The results add reduced suicidal thinking to the list of potential therapeutic benefits of targeting the brain's glutamate system.

While the research on biological markers and mechanisms holds hope for development of more practical medications in the long term, questions remain about whether there might be a limited role for ketamine itself in the short term.

In a recent assessment of the state of the science, Zarate and American and European colleagues propose that intravenous ketamine may prove useful for acutely suicidal patients who receive treatment in hospital emergency rooms. It may also offer an alternative to ECT, long considered the treatment of last resort for treatment resistant depression, but fraught with concerns about cognitive side effects.

However, the researchers recommend against the use of ketamine outside of a hospital setting, citing potential cardiovascular and other risks. They note that anesthesiologists participate in the trials at NIMH and Mount Sinai School of Medicine, New York City which also require a 24-hour inpatient stay following drug infusion.

Among about 163 patients who have been studied to date, the drug has been well tolerated and seems a reasonable treatment option for most treatment resistant depressed patients, say the researchers. Studies are under way using nasally administered ketamine and other strategies to determine how the rapid antidepressant affect might best be sustained.

"We are investigating ketamine in multiple ways — studying genes, gene expression, synapses, cells, circuits, and symptoms with neuroimaging, genetics, electrophysiological measures and other techniques," explained

Zarate. "These studies hold hope for predicting the likelihood of response and for gaining insights into mechanisms of action."

More information:

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