Metabolite created as the body breaks down ketamine is responsible for its rapid antidepressant action explains Dr. Todd Gould from the University of Maryland School of Medicine.

Typical uses for ketamine include as an anesthetic or sedative, and as a recreational drug. So it might be a surprise to learn that over the past decade ketamine has excited researchers by proving to have powerful antidepressant effects. Unfortunately, research into the use of ketamine as an antidepressant has been hindered by its unwanted dissociative, anesthetic, and addictive side effects.

Now, Panos Zanos, Todd Gould, and their team at the University of Maryland School of Medicine and intramural programs of the National Institute of Mental Health (NIMH), the National Center for Advancing Translational Sciences (NCATS), and the National Institute on Aging (NIA) have isolated the chemical byproduct produced as the body breaks down ketamine that has rapid antidepressant action. What’s more, this metabolite singularly reversed depressive behavior in mice without the aggravating side effects.

The recent study builds upon previous clinical trials that have highlighted the antidepressant potential of ketamine. In fact, clinical trials have shown that the versatile drug typically lifts depression in hours or less and a single dose can continue to have effect for over a week. Traditional antidepressants typically take weeks to exert any therapeutic actions and require daily adherence to maintain efficacy. Ketamine works robustly in patients who have failed trials with traditional antidepressants. Repeatedly though, despite promising results, these previous trials have hit a wall: the euphoric and addictive effects of ketamine could encourage abuse of the drug, hence it only has limited applications.

Fighting depression with Ketamine

With a focus on interdisciplinary research, Associate Professor Todd Gould holds appointments in Psychiatry, Anatomy and Neurobiology, and Pharmacology at the University of Maryland School of Medicine. His long-term research goal is to “conduct high quality translational research that will yield outcomes with tangible benefits to patients suffering from mood disorders.”

Gould devotes some of his time to the university’s Translational Research Laboratories, which bring together clinician scientists and basic scientists who share a common interest in translational neuroscience research to improve the lives of those who suffer from mental illness. Their shared space includes molecular and cellular biology labs, areas devoted to behavioral pharmacology, and joint procedure space for conducting neuroscience research.

Alongside their groundbreaking study into the antidepressant properties of ketamine, the team are currently working on defining the molecular mechanisms whereby lithium ions exert their therapeutic effects, studies with mice that harbour the mood disorder susceptibility gene CACNA1C, and investigating the behavioral and potential therapeutic profile of a novel beta-estradiol prodrug.

Gould is cautiously optimistic that a new generation of rapid-acting antidepressants, derived from ketamine, may be just around the corner. If all goes well, clinical trials could begin in the next 2 or 3 years. He comments that interdisciplinary collaboration has been “central to the project.”

RESEARCH FOCUS

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an antidepressant typically in a clinic setting.

To overcome this problem the research team needed to investigate in more detail how ketamine relieves depression. In the past, it had been commonly assumed that this must involve the blocking of N-methyl-D-aspartic acid (NMDA) glutamate receptors. This explanation was logical as the NMDA receptor is the previously identified anesthetic target of ketamine. However, Gould’s team knew that ketamine is rapidly processed in the body to a number of metabolites that are pharmacologically different from the original chemical. Researchers Irving Wainer and Ruin Moaddel from the National Institute on Aging (NIA) previously identified stereoisomers of (2S,6S;2R,6R)-hydroxynorketamine (HNK) as potentially important.

ISOLATING THE METABOLITE

Although the mechanism of its antidepressant effect is yet to be wholly understood, the team proved that (2S,6S;2R,6R)-HNK plays an important role. The test involved altering some ketamine molecules by replacing a hydrogen atom with a deuterium atom, a slightly heavier isotope of hydrogen. Doing so largely prevented the ketamine’s metabolism to (2S,6S;2R,6R)-HNK, while NMDA receptor blocking was unaffected. The team observed that this altered ketamine did not induce antidepressant actions in key behavioural tests 24 hours after administration, suggesting that (2S,6S;2R,6R)-HNK is a critical part of the drug’s action.

Ketamine comes in two molecular forms that are a mirror image of each other, known as enantiomers, denoted (S) and (R) ketamine. Similarly, the metabolites of ketamine also include different enantiomers, hence both are noted when writing (2S,6S;2R,6R)-HNK. On testing these mirrored molecules separately with behaviour tests in mice the research team found that one, (2R,6R)-HNK, had more potent antidepressant effects that act early and last for at least three days. Notably, this chemical was not found to inhibit NMDA receptors, instead activating a different type of glutamate receptor: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA).

Amazingly, the mice treated with the (2R,6R)-HNK metabolite could receive up to 40 times the antidepressant dose of ketamine without side effects. Additionally, when presented with a mouse size lever that would dispense more of the metabolite, they did not tend to self-administer the drug, suggesting it has little addictive effect. They did, for comparison, self-administer ketamine when given the chance.

A NEW GENERATION OF RAPID-ACTING ANTIDEPRESSANTS

Crucially, this study may explain why much of the depression clinical trial research focused on the blocking of NMDA receptors has had disappointing results, says Gould. This may be disconcerting for companies who have spent a lot of money attempting to develop drugs from ketamine based on this mechanism. However, the door is now open for further research into the role of AMPA receptors, potentially holding the key to a new generation of rapid-acting antidepressants.

Moreover, the collaboration on this project between NIH researchers and NCATS chemists demonstrates the power of interdisciplinary research. “Overall, our collective efforts exemplify how a collaborative, team science approach can help advance the translational process in ways that help get more treatments to more patients more quickly,” comments Christopher Austin, Director of the National Center for Advancing Translational Sciences (NCATS).

Now the focus is on rolling out human trials, a process that Gould warns could take a number of years. The development team, working with Dr Craig Thomas at the NCATS, are currently carrying out safety and toxicity studies of the metabolite to prepare a clinical trial for the treatment of depression with Dr Carlos Zarate at the National Institute of Mental Health (NIMH). The race is on to replicate the impressive antidepressant action of this ketamine metabolite in humans.

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