Repurposed Drug for Amplifying the Anti-Depressant Effects of Ketamine

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Overview

Psychiatric disorders, with emphasis on major depressive disorder (MDD), are leading causes of disability and premature death across the globe, with patients showing a heightened risk of self-harm and suicidal ideation. Current pharmaceutical treatment options suffer from significantly prolonged time to response and suboptimal responses in a significant proportion of the patient population. Prof. Alon Chen and his team identified a novel target of ketamine, a drug commonly prescribed to manage mood disorders. The team found that combination therapy comprised of ketamine and an agonist drug enhancing the activity of the novel target boosted antidepressive effects of ketamine in mice and propose its potential in improving current treatment protocols for psychiatric disorders, including depressive disorders MDD.

Background and Unmet Need

Major depressive disorder (MDD) is the third-leading cause of disease burden and the most common cause of disability and premature death in the general population. While clearly effective, available antidepressive drugs are significantly limited by time-to-response of up to 8 weeks, a latency period that increases the risk of suicide and self-harm. In parallel, 30-50% of patients display inadequate responses or suffer from remission. Moreover, their long-term use is often associated with side effects that further increase the risk profile of this fragile patient population. In particular, a one-time intravenous dose of ketamine, a potent glutamate N-methyl-D-aspartate (NMDA) receptor blocker, elicits a rapid and sustained antidepressant response, even among treatment-resistant patients, and effectively manages suicidal ideation. Spravato, an intranasal formulation of estketamine, was recently approved by the FDA for treatment-resistant depression. Yet, its chronic use is associated with hallucination, impaired sensory perception, and risk of addiction, raising concerns regarding it extensive use, particularly in unsupervised outpatient settings. Overall, these limitations increase risk of self-harm and suicide in MDD patients, highlighting the dire need for fast-acting agents with an acceptable safety profile.

The Solution

Ketamine-based combination treatment to amplify the antidepressive effect of ketamine while minimizing side effects

Technology Essence

In their pursuit of the molecular basis of the antidepressive effect of ketamine, this team of researchers identified its role in upregulating expression levels of a novel target in glutamatergic neurons of the ventral hippocampus of mice. The target is involved in the generation of a signature M-current that regulates overall neuronal excitability in the brain and has recently been implicated in the pathophysiology of stress-related disorders, with a positive

correlation between its expression and resilience to stress. This team found that knockdown of this target in the ventral hippocampus of mice eliminated the antidepressant effects of ketamine, as measured by immobile time in a forced swim test. Similarly, its pharmacological manipulation with a selective and potent channel antagonist, abolished the antidepressive effect of ketamine. In contrast, coadministration of ketamine and a selective activator of the target, augmented the antidepressive effect of ketamine in mice, as demonstrated by significantly less immobile time in a forced swim test as compared to untreated mice and mice treated with ketamine only.

Applications and Advantages

- Combination therapy for ketamine-based antidepressants
- Improved efficacy of ketamine-based antidepressant regimes, especially for treatment-resistant depression
- Improved safety profile of ketamine-based antidepressant regimes

Development Status

The enhanced effectiveness of ketamine in combination with agonists of the newly identified target protein has been demonstrated ex-vivo in extracted glutamatergic neurons and validated in ex-vivo electrophysiological recording analyses, as well as in vivo by monitoring animal behavior following combination treatment with pharmacological agonists and antagonists.