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Novel Ketamine Metabolites for Treating Depression, Anxiety & Addiction

Overview

UMB inventors from Prof. Todd Gould's lab, along with their collaborators, made the pivotal discovery in 2016 that certain stable ketamine metabolites exerted antidepressant actions via a different mechanism (independent of NMDAR inhibition), which made these compounds excellent drug candidates, without the negative side effects associated with ketamine therapy (Zanos et al., 2016 Nature). Their discovery led to a Phase I clinical trial (ID# NCT04711005) currently ongoing to test the safety and pharmacokinetics of antidepression drug candidate (2R,6R)-hydroxynorketamine, administered by IV infusion to healthy volunteers.

In their continuing laboratory studies of the properties of ketamine metabolites (i.e., 12 unique hydroxynorketamines or HNKs), the inventors observed an association between the 3-dimensional structures of compounds and their relative potencies to induce antidepressant-relevant behavioral effects in the forced swim test in male mice. The inventors synthesized & tested further compounds to explore their structure-activity hypothesis, including (5R)-methyl-(2R,6R)-HNK, which exhibited promising antidepressant-like potency. UMB (in collaboration with NIH) is pursuing patent protection for composition of novel small molecules and their method of use for treating depression, anxiety, addiction, and related disorders.

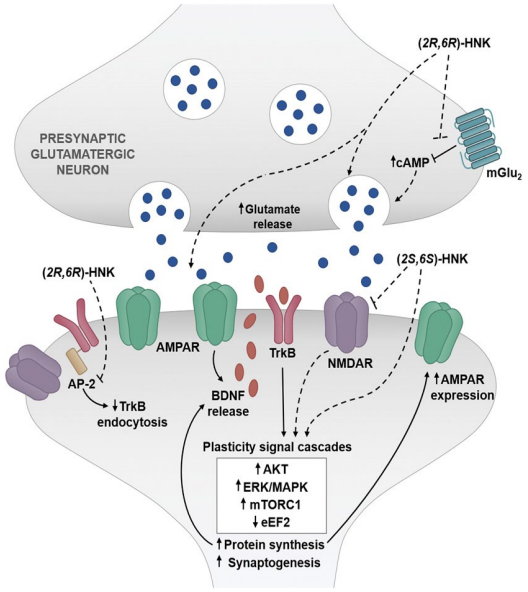

FIGURE: Putative synaptic mechanisms of (2R,6R)- and (2S,6S)-hydroxynorketamine (Highland et al, 2021)

Investigators

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Description

Small molecule; ketamine-related; depression; addiction

Field

Antidepression treatment

Advantages

- Novel small molecules
- Predict favorable drug properties
- Inventors with clinical drug development experience

Technology Status

Available for licensing & sponsored research

Patent Status

Patent pending (WO 2022/047256)

UMB Docket#

TG-2021-015

References

Highland et., ACS Chem Neurosci. 2022 Feb 16;13(4):510-523.

Highland et al., Pharmacol Rev. 2021 Apr;73:763-791.

Zanos et al., Nature. 2016;533:481-486.

Market & Applications

Major depressive disorder is common, affecting about 16% of the world population at some point in their lives, and is associated with serious health and socioeconomic consequences. Current pharmacotherapies require prolonged administration (weeks if not months) for clinical improvement. This lag time, as well as a high non-response rate, emphasizes the need for better antidepressant medications. Ketamine has demonstrated rapid and robust efficacy as an antidepressant by improving core depressive symptoms including depressed mood, anhedonia, and suicidal thoughts in treatment-refractory unipolar and bipolar depressed patients when administered at sub-anaesthetic doses. However, its potential for widespread clinical use is limited owing to its abuse liability and capacity to produce dissociative effects even when administered at low doses. There remains a critical need for novel, potent drug candidates for the treatment of depression, as well as addiction and related disorders.

Stage of Development

Published proof-of-concept data for novel compounds in antidepressant-relevant animal model.

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