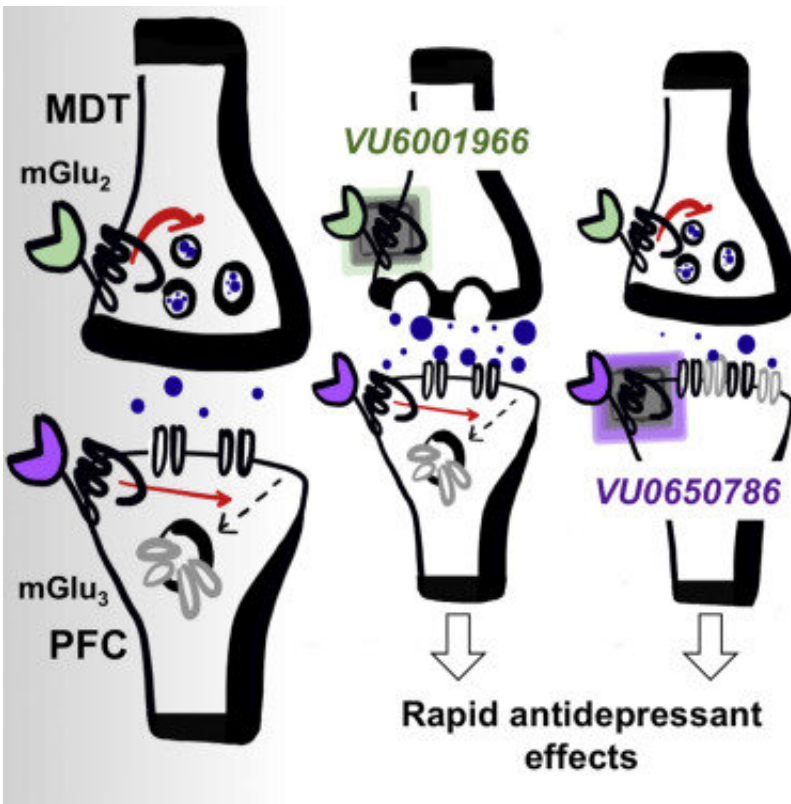


Study explores potential new class of antidepressants

November 25 2019, by Bill Snyder



Graphical Abstract. Credit: *Neuron*

Researchers at Vanderbilt University Medical Center have taken a major step that could ultimately facilitate development of a new class of antidepressants which may relieve symptoms more rapidly and effectively and with fewer side effects than current medications.

Their approach involves increasing the supply of the excitatory neurotransmitter [glutamate](#) in a part of the brain that modulates mood by turning down the activity of receptors which inhibit glutamate release.

Reporting last week in the journal *Neuron*, Max Joffe, Ph.D., P. Jeffrey Conn, Ph.D., and colleagues blocked long-term changes in glutamate release in an animal model with druglike molecules that selectively inhibited either mGlu2 and mGlu3, glutamate receptors located on opposite sides of the synapse, or gap, between nerve cells.

"Depression is not a single disorder," said Conn, who directs the Vanderbilt Center for Neuroscience Drug Discovery. "As we learn more, we may find out that mGlu2 and mGlu3 have utility in different aspects of depression. Different patients may respond better to one than the other."

The compounds affected [neural circuitry](#) connecting the prefrontal cortex of the brain to the thalamus. While this circuitry is involved in attention and cognitive function, it also is "extremely important for these rapid antidepressant actions," said Joffe, a postdoctoral fellow in Pharmacology and the paper's first author.

The most commonly prescribed antidepressants, called SSRIs, selectively inhibit the reuptake of another neurotransmitter, serotonin. But they can take several weeks to relieve symptoms, anxiety is a common side effect and a third of patients don't respond to the drugs.

Ketamine, initially developed as an anesthetic, recently has been touted for its ability to rapidly relieve depression, potentially by releasing a "burst" of glutamate. But treatment must be carefully monitored because the drug can trigger hallucinations and other psychotic symptoms.

Another possible way to "jolt" the brain out of depression may be to

increase glutamate in the prefrontal cortex by turning down the activity of specific types of glutamate receptors that inhibit its release.

Conn, the Lee E. Limbird Professor of Pharmacology in the Vanderbilt University School of Medicine, is a leader in the field of "metabotropic" glutamate receptors, which play important roles in cognition, memory and movement, and in disorders such as schizophrenia, Alzheimer's and Parkinson's disease.

Metabotropic receptors are membrane receptors that act through second messengers.

Over the years Conn and his colleagues have developed a series of compounds called "allosteric" modulators that act like dimmer switches in electrical circuits, dampening or enhancing glutamate transmission in specific brain circuits without causing side effects elsewhere.

Conn credited the National Institutes of Mental Health and the National Institute of Neurological Disorders and Stroke within the National Institutes of Health (NIH) as well as the Pharmaceutical Research and Manufacturers of America (PhRMA) Foundation with supporting this work.

They also have promoted the development of tools that have enabled the "mapping out" of specific cell populations involved in various aspects of behavior and disease, he said.

Using these and other tools, the Vanderbilt researchers showed that compounds which dampen mGlu2 or mGlu3 activity "enhance thalamocortical transmission and inhibit long-term depression but do so by mechanistically distinct presynaptic and postsynaptic actions."

"We're just starting to really understand how mGlu3 and mGlu2 differ

and how they may be uniquely relevant for specific patient populations that have different aspects of depression," Conn said.

More information: Max E. Joffe et al. mGlu2 and mGlu3 Negative Allosteric Modulators Divergently Enhance Thalamocortical Transmission and Exert Rapid Antidepressant-like Effects, *Neuron* (2019). [DOI: 10.1016/j.neuron.2019.09.044](https://doi.org/10.1016/j.neuron.2019.09.044)

Provided by Vanderbilt University

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