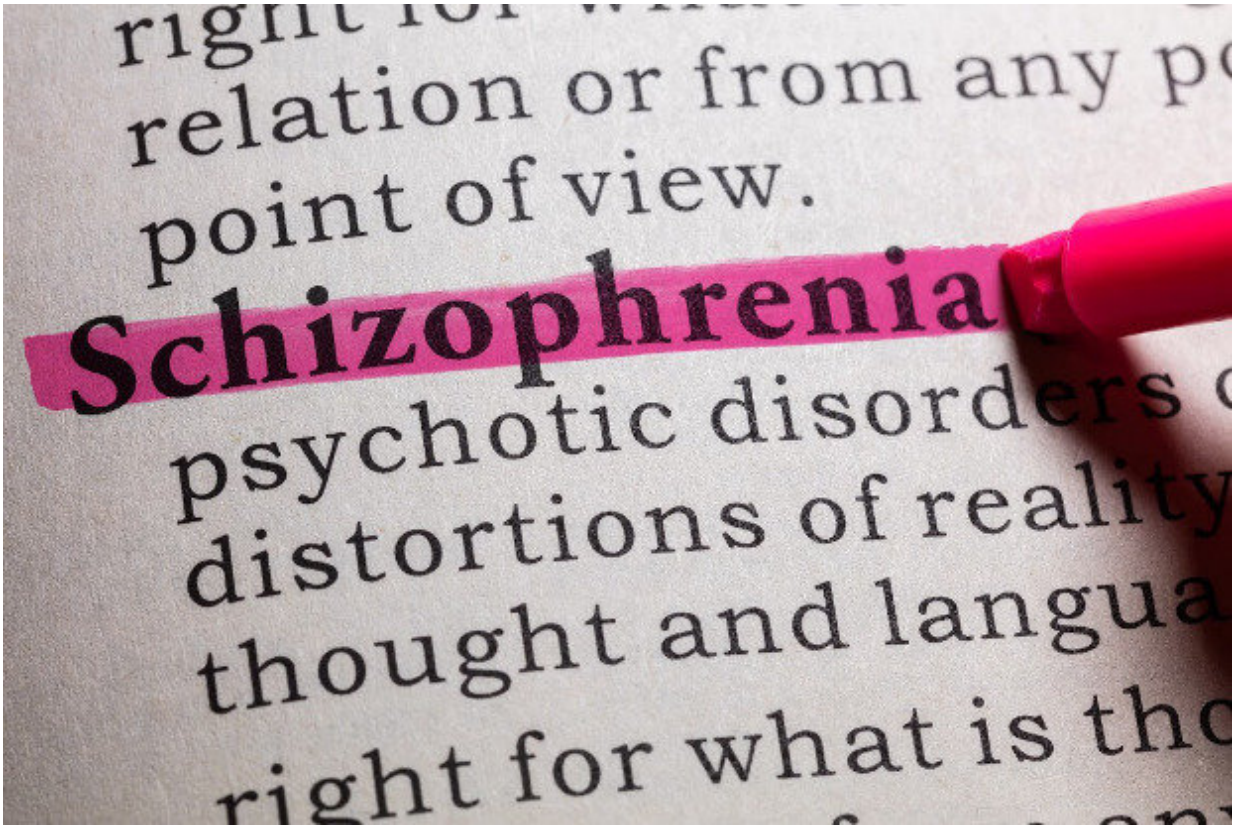
Scientists researching drugs that could improve brain function in people with schizophrenia

October 12 2017, by Leah Small



Credit: Virginia Commonwealth University

Virginia Commonwealth University researchers are testing if drugs known as HDAC inhibitors improve cognition in patients with

schizophrenia who have been treated with the antipsychotic drug clozapine.

Clozapine, which has been shown to be the most effective available antipsychotic for hallucinations and delusion treatment, may impair memory and attention, said Ananda Pandurangi, M.D., medical director and chair of inpatient psychiatry in the Department of Psychiatry at VCU School of Medicine. Pandurangi is an investigator on the clinical trial.

"By improving symptoms associated with schizophrenia such as hallucinations and behavior disorder, clozapine indirectly improves cognition," Pandurangi said. For example, he said, a person who is not hallucinating can better concentrate and interact with others, which provides social stimulation that enhances cognition. However, Pandurangi added, clozapine may diminish individual cognitive functions such as short-term memory.

Researchers hypothesize that HDAC inhibitors, which repress the functions of a specific family of proteins, could prevent an adverse mechanism that results from clozapine's interaction with the brain.

"Clozapine's potential to further benefit memory, attention and other aspects of cognition may be constrained by one of its own actions, which HDAC inhibitors could prevent," Pandurangi said.

Clozapine and the brain

Javier González-Maeso, Ph.D., associate professor of physiology and biophysics at VCU School of Medicine, discovered the mechanism that HDAC inhibitors would target. He first noticed an increase in the protein HDAC2 that may result from chronic treatment of schizophrenia with clozapine. He then found that inhibiting the function of HDAC2 in

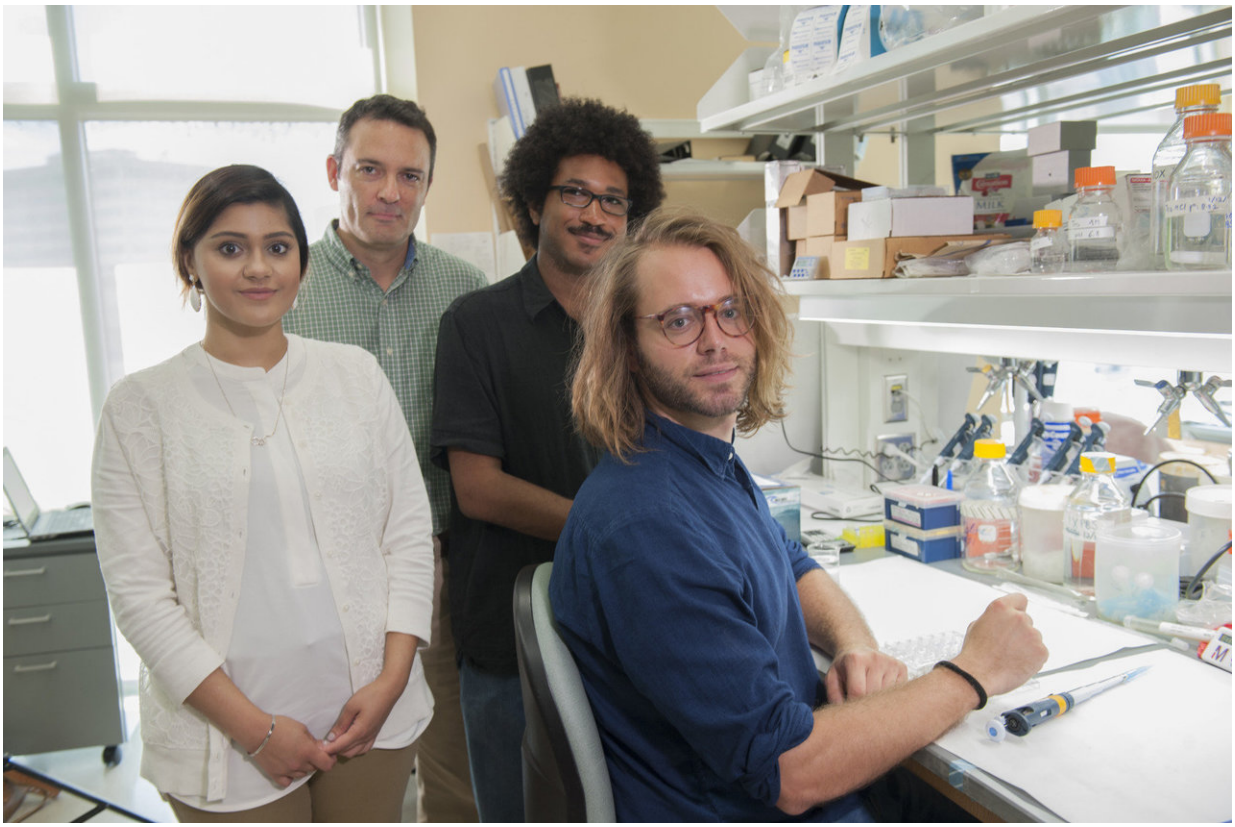
associated neurons may improve cognition.

HDAC2 is one of a group of proteins that makes potentially inheritable changes to the way a gene impacts observable characteristics of an individual, such as behavior.

González-Maeso and Pandurangi are currently recruiting people with schizophrenia for a pilot study to test the effectiveness of the drug vorinostat, which is currently used to treat skin cancer, as an HDAC2 inhibitor. The study will be the start of determining if HDAC2 could be a new target for schizophrenia treatment.

"In post-mortem samples of patients, we found the same pathway that was affected by clozapine in mice was in the frontal cortex of people with schizophrenia who had been treated with antipsychotics," González-Maeso said.

González-Maeso's work was published in the journal *Nature Neuroscience* in August and is funded by the National Institute of Mental Health. Researchers at the Icahn School of Medicine at Mount Sinai in New York and the University of the Basque Country in Bilbao, Spain, contributed to initial experiments on mice and post-mortem human samples.



Members of González-Maeso lab group, who worked extensively on the published findings, from left to right: Maryum Ijaz, Javier González-Maeso, Ph.D.; Justin Saunders, Mario de la Fuente Revenga, Ph.D. Credit: Tom Kojcsich, University Marketing

González-Maeso began testing vorinostat for its impact on cognition due to the drug's known ability to inhibit proteins that belong to the HDAC family. It is possible that more specific HDAC inhibitors could be tested because much is still unknown about vorinostat's effectiveness for the newly identified potential use.

If the researchers are able to further prove the concept through human trials, people with schizophrenia could avoid psychosis while improving cognitive function.

"Schizophrenia is a devastating disease," González-Maeso said. "The cognitive dysfunction in schizophrenia is one of the core impairments that negatively affect quality of life for these patients. Life would be so much better for our patients with a drug that treated cognitive dysfunction."

Finding the key

A discovery by González-Maeso published in *Nature Neuroscience* in 2012 laid the groundwork for the investigation of vorinostat's capabilities. The scientist found when HDAC2 increases in the brain after chronic clozapine treatment, it impairs glutamate, which is involved in cognition and other functions and is the most abundant neurotransmitter in the body. HDAC2 also reduces the functionality of the mGlu2 glutamate receptor, which has a role in memory.

"What we have is a lock-and-key mechanism," Pandurangi said. "To open the door you need a particular key. The lock is the mGlu2 receptor and the key is glutamate. HDAC2 inhibitors will make the key work better with the lock."

Testing phases

González-Maeso recently completed experiments on blocking the function of HDAC2 in mice and tested the impact of clozapine on the recognition memory of mice. These findings inform hypotheses for how HDAC2 and clozapine impact the human brain. To measure recognition memory, he set up two testing groups. One was treated chronically with clozapine and the other was a control group that was not medicated. The mice were exposed to two objects on a single day. On the following day, one of those objects was changed.

"Normal mice show curiosity for the new object and spend time exploring it," González-Maeso said.

Mice treated chronically with clozapine do not, he said.

"They cannot remember the initial object from the previous day, so they don't recognize the change," González-Maeso said.

Following completion of the first human trial, González-Maeso and Pandurangi plan to conduct large trials in collaboration with multiple institutions to continue testing the efficacy of HDAC2 inhibitors.

More information: Daisuke Ibi et al. Antipsychotic-induced Hdac2 transcription via NF-κB leads to synaptic and cognitive side effects, *Nature Neuroscience* (2017). DOI: 10.1038/nn.4616

Provided by Virginia Commonwealth University