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Researchers develop method for advancing development of antipsychotic drugs

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Researchers interested in the treatment of schizophrenia and dementia have clarified how antipsychotic drugs that target a complex of two receptors at the surface of cells in the brain work, according to a new study published online Nov. 23 in the journal *Cell*.

The multidisciplinary team included researchers from the Virginia Commonwealth University School of Medicine, together with the Mount Sinai School of Medicine in New York and the University of Maryland School of Pharmacy in Baltimore. In an earlier, but related study, the Mount Sinai School of Medicine team had shown that two brain receptors, which bind the critical neurotransmitter signals serotonin and glutamate at the outside of the cell, form a complex in the areas of the brain that malfunction in schizophrenic patients.

The team has now developed a metric that may help determine the effectiveness of antipsychotic drugs and advance drug design. The present work fills an important gap in knowledge as previously researchers did not understand how this receptor complex was connected to the phenotype of schizophrenia.

The current study findings show that the connection between the complex of the two receptors and the schizophrenic phenotype is a defect in how the serotonin and glutamate signals get interpreted at the inside of the cell, a process referred to as signaling. Moreover, it shows how antipsychotic drugs used to treat patients work to correct such a defect in the brain.

"Not only have we learned how antipsychotics drugs are effective, but we have also found that the signaling through this receptor complex is critical to how these anti-psychotics work," said the study's principal investigator Diomedes E. Logothetis, Ph.D., an internationally recognized leader in the study of ion channels and cell signaling mechanisms and chair of the VCU School of Medicine's Department of Physiology and Biophysics.

According to Logothetis, the most common cellular targets for drugs used in the clinic and by the pharmaceutical industry are G protein-coupled receptors, such as the ones that were examined in this study. Using cell and animal models, they found that the receptors signal very differently when they are together as a complex than when they are apart.

The metric developed by the team could be used to screen new drugs and determine their level of effectiveness, or be used to assess combination therapies - that is, putting two previously ineffective drugs together and making them more useful for some patients. Ultimately this work may translate to creating better antipsychotic drugs for patients.

"We can use the metric we developed to screen new drugs and determine their level of effectiveness," Logothetis said. "We can also use the metric to assess what combinations of existing drugs will give us the ideal balance between the signaling through the two receptors of the complex."

Logothetis said the hope is that by using this approach one day researchers will be able to develop a means by which high-throughput screening of drugs can be performed and they also will be able to develop more effective combinations of drugs that are able to help the third of schizophrenic patients who do not respond to current treatments.

Future studies will focus on further identifying the protein targets of the unique signaling pattern of this receptor complex and their link to schizophrenia.

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