Targeting nicotine receptors to treat cognitive impairments in schizophrenia

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Smoking is a common problem for patients with schizophrenia. The increased tendency of patients diagnosed with this disorder is to not only smoke, but to do so more heavily than the general public. This raises the possibility that nicotine may be acting as a treatment for some symptoms of schizophrenia.

Nicotine acts through two general classes of brain receptors, those with high and low affinity for nicotine. The low affinity class of nicotinic receptors contains the alpha-7 subunit, which is present in reduced numbers in people with schizophrenia.

Two papers published in the January 1st issue of Biological Psychiatry suggest that drugs that stimulate these alpha-7 subunit-containing nicotinic receptors might enhance cortical function and treat cognitive impairments associated with schizophrenia.

In their study of healthy monkeys, Graham Williams and colleagues at Yale University and AstraZeneca found that very low doses of AZD0328, a novel drug that acts as an alpha-7 agonist, produced both acute and persistent improvements in their performance on a spatial working memory task.

"Our work demonstrates that that the neuronal nicotinic alpha-7 receptor plays a critical role in the core cognitive function of working memory, which is a key indicator of outcome in patients with schizophrenia," explained Dr. Williams. "The function of the alpha-7 receptor may

account for the ability of a partial agonist to induce long-term beneficial changes for high-order cognition at such low doses."

This influence on cortical function has been exemplified by the work of Jason Tregellas and colleagues. These researchers examined the effects of DMXB-A, a novel alpha-7 partial agonist, on the brain's 'default network' in people with schizophrenia. Function of the default network, which is likely a major contributor to the intrinsic neuronal activity that accounts for 60-80% of the brain's energy use, is different in people with schizophrenia.

Dr. Tregellas summarized their findings: "We found that DMXB-A altered default network activity in people with schizophrenia in a pattern consistent with improved function of the network. We also found that these neuronal differences were related to the genotype of the alpha-7 nicotinic receptor and to drug-related improvements in symptoms."

Together, "these two studies provide additional support for a novel pharmacologic approach to treat cognitive impairments in schizophrenia ", observed Dr. John Krystal, Editor of *Biological Psychiatry*.

More information: The first article mentioned is "Immediate and Sustained Improvements in Working Memory After Selective Stimulation of α7 Nicotinic Acetylcholine Receptors" by Stacy A. Castner, Gennady N. Smagin, Timothy M. Piser, Yi Wang, Jeffrey S. Smith, Edward P. Christian, Ladislav Mrzljak, and Graham V. Williams. Castner and Williams are affiliated with the Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut, and VA Connecticut Healthcare System, West Haven, Connecticut. Smagin, Piser, Wang, Smith, Christian, and Mrzljak are from AstraZeneca Pharmaceuticals, Wilmington, Delaware.

The second mentioned article is "Effects of an Alpha 7-Nicotinic

Agonist on Default Network Activity in Schizophrenia" by Jason R. Tregellas, Jody Tanabe, Donald C. Rojas, Shireen Shatti, Ann Olincy, Lynn Johnson, Laura F. Martin, Ferenc Soti, William R. Kem, Sherry Leonard, and Robert Freedman. Tregellas, Tanabe, Rojas, Shatti, Olincy, Johnson, Martin, Leonard, and Freedman are affiliated with the Department of Psychiatry, Denver VA Medical Center, VISN19 MIRECC and University of Colorado—Denver, Aurora, Colorado. Tanabe is also from the Department of Radiology, University of Colorado—Denver, Aurora, Colorado. Soti and Kem are with the Department of Pharmacology and Therapeutics, University of Florida, Gainesville, Florida.

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