New Treatment Mechanisms for Schizophrenia

Philadelphia, PA, January 3, 2008 – The field of schizophrenia research has come alive with many exciting new potential approaches to treatment. From the introduction of chlorpromazine to the current day, all treatments approved by the U.S. Food and Drug Administration have had, at their core, a single treatment mechanism, the blockade of the dopamine D2 receptor. The introduction of clozapine in the 1980’s suggested a potential that other brain targets might complement the blockade of dopamine D2 receptors to treat symptoms that failed to respond to the “typical” antipsychotics. We are now entering an age where new treatments are being rationally developed within the context of translational neuroscience, i.e., the steps whereby basic molecular neuroscience leads to fundamental new mechanisms that can be tested in animal and human laboratory-based research that, in turn, leads to tests of new medications in our clinics. The January 1st issue of *Biological Psychiatry* includes encouraging new research related to three new treatment approaches.

In the first study, Olszewski and colleagues tested a novel drug that inhibits the breakdown of the transmitter N-acetylaspartylglutamate (NAAG), which activates a receptor that reduces schizophrenia-like behaviors in some animal models. Their findings indicate that this drug is effective in an animal model of schizophrenia. Joseph H. Neale, Ph.D., lead author on this project, comments, “While treating patients with receptor agonists can be highly effective therapy, drugs that increase the action of the transmitter that activates the same receptor have traditionally been very effective with fewer side effects than chronic agonist treatment.” He adds, “These data support the conclusion that NAAG peptidase inhibitors represent a breakthrough in the discovery of a completely novel means of adjunct therapy for schizophrenia that is analogous to the use of SSRIs [selective serotonin reuptake inhibitors] for the treatment of depression.”

In the second article, Hashimoto and colleagues demonstrated that repeated administration of the N-methyl-D-aspartate (NMDA) receptor antagonist phencyclidine (PCP) decreased the density of α7 nicotinic receptors (α7 nAChRs) in the mouse brain,
and that the novel $\alpha_7$ nAChR agonist SSR180711 could ameliorate PCP-induced cognitive deficits in mice. According to Kenji Hashimoto, Ph.D., head author for this study, the impetus for this study came from the fact that “accumulating evidence suggests that $\alpha_7$ nicotinic receptors, a subtype of nicotinic receptors, are a most attractive target for novel therapeutic drugs of neuropsychiatric diseases including schizophrenia and Alzheimer’s disease. Behavioral abnormalities in animals after repeated administration of the NMDA receptor antagonist phencyclidine (PCP) have been used an animal model of schizophrenia.” These findings suggest that $\alpha_7$ nAChR agonists including SSR180711 could be potential therapeutic drugs for cognitive deficits in schizophrenic patients.

In the third investigation, Semenova and colleagues show that a recently discovered brain receptor for serotonin (5-HT$_7$) might be of importance for understanding certain aspects of schizophrenia. Their study focused on sensory input processing, which is often impaired in schizophrenia, and finds that blockade of this particular serotonin receptor in mice alleviates this impairment. Peter B. Hedlund, M.D., Ph.D., senior author, notes: “Certain pharmaceuticals used to treat schizophrenia interact with this receptor. Our results indicate that especially so-called atypical antipsychotics may promiscuously exert some of their beneficial effects through the 5-HT$_7$ receptor. Further exploration of this receptor as a treatment target may lead to more specific and better medications for disorders such as schizophrenia.”

John H. Krystal, M.D., Editor of *Biological Psychiatry* and affiliated with both Yale University School of Medicine and the VA Connecticut Healthcare System, comments, “It is very clear that very few tested medications actually become new treatments. However, the embedding of clinical research within the framework of translational neuroscience increases the likelihood that one or another of these mechanisms might someday emerge as a treatment for schizophrenia.” Dr. Krystal concludes, “Since we have so few mechanistically distinct approaches for the pharmacotherapy of schizophrenia, the possibility of the emergence of new treatment mechanisms is certainly a source of hope.”

Notes to Editors:
The first article is “Phencyclidine and Dizocilpine Induced Behaviors Reduced by N-acetylaspartylglutamate Peptidase Inhibition via Metabotropic Glutamate Receptors” by Rafal T. Olszewski, Marta M. Wegorzewska, Ana C. Monteiro, Kristyn A. Krolikowski, Jia Zhou, Alan P. Kozikowski, Katrice Long, John Mastropaolo, Stephen I. Deutsch and
Joseph H. Neale. Drs. Olszewski, Węgorzewska, Monteiro, Krolikowski, and Neale are from the Department of Biology, while Dr. Deutsch is from the Department of Psychiatry, at Georgetown University, Washington, D.C. Drs. Long, Mastropaolo, and Deutsch are affiliated with the Mental Health Service Line, Department of Veterans Affairs Medical Center, Washington, D.C. Drs. Zhou and Kozikowski are with Acenta Discovery Inc., Tucson, Arizona. Dr. Kozikowski is also affiliated with the Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, Illinois.

The second article is “Phencyclidine-Induced Cognitive Deficits in Mice Are Improved by Subsequent Subchronic Administration of the Novel Selective $\alpha_7$ Nicotinic Receptor Agonist SSR180711” by Kenji Hashimoto, Tamaki Ishima, Yuko Fujita, Masaaki Matsuo, Tatsuhiko Kobashi, Makoto Takahagi, Hideo Tsukada and Masaomi Iyo. Drs. Hashimoto, Ishima, and Fujita are affiliated with the Division of Clinical Neuroscience, Chiba University Center for Forensic Mental Health, Chiba, Japan. Drs. Matsuo, Kobashi, and Takahagi are with the Nard Institute, Amagasaki, Hyogo, Japan. Dr. Tsukada is affiliated with the PET Center, Central Research Laboratory, Hamamatsu Photonics K.K., Hamamatsu, Shizuoka, Japan. Dr. Iyo is from the Department of Psychiatry, Chiba University Graduate School of Medicine, Chiba, Japan.

The third article is “Inactivation of the 5-HT7 Receptor Partially Blocks Phencyclidine-Induced Disruption of Prepulse Inhibition” by Svetlana Semenova, Mark A. Geyer, J. Gregor Sutcliffe, Athina Markou and Peter B. Hedlund. Drs. Semenova, Geyer, and Markou are affiliated with the Department of Psychiatry, University of California San Diego in San Diego, California. Drs. Sutcliffe and Hedlund are from the Department of Molecular Biology at The Scripps Research Institute, La Jolla, California.

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Full text of the articles mentioned above are available upon request. Contact Jayne M. Dawkins at (215) 239-3674 or ja.dawkins@elsevier.com to obtain a copy or to schedule an interview.

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