



Glutamate and the Pharmacotherapy of Schizophrenia

John H. Krystal, M.D.

*Albert E. Kent Professor and Deputy Chairman for Research
Department of Psychiatry, Yale University School of Medicine*

Q What is glutamate?

A Glutamate is the main excitatory chemical messenger of the cerebral cortex and limbic system, the parts of the brain responsible for mental functions and emotions.

Q What does it inhibit? Stimulate?

A Glutamate is excitatory; and it stimulates both inhibitory and excitatory nerve cells in the brain. Glutamate also coordinates activity of groups of nerve cells or “networks” in the brain.

Q What is the difference between it as a brain messenger and NE or DA?

A NE or DA are modulators that tune up or down glutamate cells in the brain. Glutamate is also one of the chemicals that activate NE or DA cells. When we think of DA or NE effects on the brain, it is usually the effects of these transmitters on glutamate cells or cells that release the inhibitory chemical messenger, GABA.

Q What medications are glutamate enhancers?

A Agents used to strengthen glutamate effects have received relatively little clinical study. There are several classes of these drugs that are being tested to enhance mental function, but they are all still experimental.

Q What is the role of glutamate in drug abuse?

A Well, we have learned that phencyclidine (PCP) and Ketamine block a subtype of glutamate receptor in the brain. These types of drugs are anesthetic agents that have both euphoric and cognitive effects when taken at sub-anesthetic doses. Alcohol also blocks this glutamate receptor and, as a result, shares many effects with PCP or ketamine. For example, alcohol dependent patients describe similarities in the effects of ketamine and alcohol. It turns out that the glutamate system in the brain is involved in many facets of addiction: anticipation, experience of reward, tolerance, dependence and withdrawal. For drugs like opiates and cocaine, that do not have direct action at glutamate receptors, this link to glutamate highlights the modulator roles of DA & NE on glutamate, mentioned earlier.

Q What percent of the brain messengers do you think we have discovered so far?

A We don't know yet. We are discovering new messengers and new proteins that are involved in the response to those messengers at very high rates. There is still much to be discovered about the brain, psychiatric illness and addiction.

Q Could you briefly describe the “PCP model” of schizophrenia?

A Briefly, it appears schizophrenia is associated with disturbance in cortical communication and abnormalities in glutamate and GABA nerve cells. DA may also be affected. PCP may mimic some of the disturbances in brain networks that are associated with schizophrenia. As a result, blocking some glutamate receptors may produce effects in healthy people that resemble aspects of schizophrenia. The principle value of the PCP model is probably that it is a tool that can be used to examine what happens in the brain when a very specific disturbance in glutamate regulation occurs. We can use this model in controlled ways to study illness mechanisms and treatments that might be relevant to schizophrenia. We have already seen evidence that this model is generating new and unexpected hypotheses promising novel agents for the treatment of schizophrenia. However, it is extremely important not to confuse the model and the illness; we

know that schizophrenia is a complicated disorder that cannot be explained simply as a disturbance in one type of glutamate receptor.

Q Schizophrenic patients have high rates of co-morbid substance use disorders. Is this because they are self medicating? What has your research shown?

A The work of my collaborators, particularly Drs. Cyil D'Souza, Ismene Petrakis, and Leslie Jacobsen, suggests that there are similarities and differences in the way certain drugs of abuse effect schizophrenia. The neurobiology of schizophrenia may be a risk factor for addiction, but the addiction that develops may share many features of addictions in other groups. In most cases, ethanol, THC, and nicotine produce euphoria in schizophrenic patients as they do in other groups of people. The neurobiology of addictive disease in these patients is not necessarily self-medication. By self-medication, I mean the attempt to treat the symptoms of schizophrenia with a drug of abuse. As a challenge to the self-medication hypothesis, I think that clinicians commonly find that alleviation of schizophrenic symptoms does not stop addiction. Often, focused intervention is needed to treat substance abuse in these patients, not unlike other groups with addictions. This is not to say that self-medication does not occur, but rather to emphasize the importance of treating addictions in schizophrenic patients as major foci of treatment. Emphasis on self-medication models has tended to de-emphasize the importance of addiction treatment, in relationship to treating schizophrenic symptoms.

Q What types of studies are underway at the CTNA?

A The Center for the Transnational Neuroscience of Alcohol was created to bridge the gap perceived in alcohol research. We brought together a large body of basic science and clinical research aimed at treatment. We gathered groups from Columbia, the University of Texas Southwestern Medical Center, and Yale to track mechanisms from basic science research through human lab research with an emphasis on psychopharmacology, neuroimaging and molecular genetics, or put more broadly, molecular neuroscience.

Q What do you plan to study in the future?

A Melancholic and psychotic patients with major depressive disorder demonstrate a reduction in occipital cortex GABA levels. These reductions are not observed in bipolar depressed patients or patients with atypical depression. Electro convulsive therapy and antidepressant treatment raise GABA levels in depressed patients, suggesting that normalizing GABA function may contribute or reflect effective antidepressant treatments. Mood-stabilizing anticonvulsant medications raise cortical GABA levels in patients with seizure disorders, and are associated with seizure control. Thus, GABA systems may also be a target for the treatment of bipolar disorder.

For the past several years, my laboratory has consisted of a closely-knit consortium of faculty, fellows, and advanced residents employing psychopharmacologic, electro physiologic, functional magnetic resonance imaging (fMRI), and magnetic resonance spectroscopic (MRS) techniques to characterize normal human cortical glutamate and GABA function and pathological changes associated with major psychiatric illnesses. My research has primarily applied these techniques to the study of schizophrenia and alcoholism. This work began in the early 1990's with our "rediscovery" of the psychokinetic, cognitive and perceptual effects of the NMDA glutamate receptor antagonist, ketamine, in healthy subjects. We became interested in the role of glutamate systems in information processing in cortico-thalamic circuits. We then evaluated these processes employing clinical research paradigms that permitted us to study these circuits most directly. Similar studies conducted in schizophrenic patients have enabled us to make tentative bridges between pharmacological models and the putative pathophysiology for this disorder. We hope to build from our psychopharmacologic studies in healthy subjects to novel treatments for schizophrenia.

Florida Recovery Center



Kenneth Thompson, M.D.-Medical Director
Scott Teitelbaum, M.D.-Clinical Director
 (352) 265-5411
frc@shands.org



Editor in Chief
 Mark S. Gold, M.D.

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