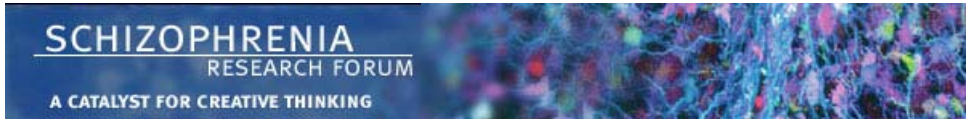

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Current Hypotheses

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Glutamate Hypothesis of Schizophrenia

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The glutamate hypothesis of schizophrenia posits that the function of the N-methyl-D-aspartate (NMDA) receptor is compromised in this disease. NMDA receptors are a major subtype of glutamate receptors and mediate slow excitatory postsynaptic potentials (EPSPs). These slow EPSPs are considered critical for the proper expression of complex behaviors, such as associative learning, working memory, behavioral flexibility, and attention, many of which are impaired in schizophrenia. NMDA receptors also play an essential role in the development of neural pathways, including pruning of cortical connections during adolescence, making them a critical component of developmental processes whose malfunction may lead to schizophrenia.

Glutamate is the major excitatory neurotransmitter in the central nervous system. Nearly half of the neurons in the brain, including *all* neurons that project from the cerebral cortex, are believed to use glutamate as their neurotransmitter. Glutamate receptors are classified into two broad categories: ionotropic and metabotropic receptors. Ionotropic glutamate receptors, which include NMDA, kainate, and AMPA subtypes, initiate rapid depolarization by facilitating sodium or calcium entry into neurons through channels formed by the receptor itself. NMDA receptor channels are permeable to calcium and are unique in being "doubly gated" by voltage and ligands, meaning that they are activated when the binding of glutamate *coincides* with a depolarizing shift in the membrane potential. Metabotropic glutamate receptors, termed mGlu1 through mGlu8, modulate neurotransmission by activating G-protein coupled synaptic transduction mechanisms. Some mGlu receptors, in particular the mGlu5 subtype, interact closely with NMDA receptors and may directly modulate the function of the NMDA receptor channel.

The idea of a glutamatergic abnormality in schizophrenia was first proposed by Kim, Kornhauber, and colleagues in 1980 (Kim et al., 1980) based on their findings of low cerebrospinal fluid (CSF) glutamate levels in patients with schizophrenia. This theory was not received well because, first, these findings could not be replicated in subsequent studies and, second, our limited knowledge of the glutamate system at the time suggested that disruptions in glutamate neurotransmission would result in overt toxicity and gross developmental abnormalities, something not seen in schizophrenia. In the last two decades, however, basic and clinical evidence has been accumulating to support the idea that aberrant NMDA receptor function subserves many aspects of molecular, cellular, and behavioral abnormalities associated with schizophrenia. These include the following:

1. Recreational use or investigator administration of a single low dose of an NMDA receptor antagonist such as phencyclidine (PCP) or ketamine produces "schizophrenialike" symptoms in healthy individuals and profoundly exacerbates preexisting symptoms in patients with schizophrenia (Javitt et al., 1991; Krystal et al., 1994; Lahti et al., 1995). The range of symptoms produced by these agents resembles positive (delusion and hallucination), negative (avolition, apathy, and blunted affect), and cognitive (deficits in attention, memory, and abstract reasoning) symptoms of schizophrenia, as well as disruptions in smooth-pursuit eye movements and prepulse inhibition of startle. Furthermore, direct comparison of healthy volunteers receiving subanesthetic doses of ketamine and individuals with schizophrenia shows similar disruptions in working memory and thought disorder between the two groups (Adler et al., 1999), suggesting that deficient activation of NMDA receptors may be a critical component of the cognitive deficits observed in schizophrenia.

2. The majority of the genes that have recently been associated with an increased risk for schizophrenia can influence the function of modulatory sites on the NMDA receptor or intracellular-receptor interacting proteins that link glutamate receptors to signal transduction pathways (Harrison et al., 2003; Moghaddam, 2003). These include association with schizophrenia of allelic variants of genes for neuregulin 1 (Stefansson et al., 2002), which can influence the expression of NMDA receptors through activation of Erb4 receptors, and GRM3, which encodes the mGlu3 subtype of metabotropic glutamate receptors (Egan et al., 2004).

3. Postmortem studies show changes in glutamate receptor binding, transcription, and subunit protein expression in the prefrontal cortex, thalamus, and hippocampus of subjects with schizophrenia (Clinton and Meador-Woodruff, 2004). Examples include decreases in NR1 subunits of the NMDA receptor in hippocampus and frontal cortical areas, high expression of excitatory amino acid transporters (EAAT) in the thalamus, and changes in the NMDA receptor-affiliated intracellular proteins such as PSD95 and SAP102 in the prefrontal cortex and thalamus.

4. Levels of amino acids N-acethylaspartate (NAA) and N-acethylaspartylglutamate (NAAG), and the activity of the enzyme that cleaves NAA to NAAG and glutamate are altered in the CSF and postmortem tissue from individuals with schizophrenia (Tsai et al., 1995). NAAG is an endogenous ligand for the mGlu3 subtype of glutamate receptor, the gene for which has been implicated in increased propensity to develop schizophrenia. Furthermore, reduced NAA levels are thought to reflect decreased glutamate availability.

5. Recent imaging studies using a novel SPECT tracer for the NMDA receptor (123I)CNS-1261 (Pilowsky et al., 2005) have reported reduced NMDA receptor binding in the hippocampus of medication-free patients. While this study remains to be replicated in a larger group of patients, it represents the first direct demonstration of NMDA receptor deficiency in schizophrenia.

6. Glutamate neurons regulate the function of other neurons that have been strongly implicated in the pathophysiology of schizophrenia. These include GABA interneurons whose morphology has been altered in schizophrenia (Lewis et al., 2005), and dopamine neurons, which are the target of antipsychotic drugs. For example, bursting of dopamine neurons, which is thought to be an integral component of their proper response to environmental stimuli, is dependent on activation of NMDA receptors on these neurons (Johnson et al., 1992). Along the same lines, it is noteworthy that two key pharmacological clues to the pathophysiology of schizophrenia—clinical efficacy of D2 receptor antagonist and increased probability of developing schizophrenia after cannabis use during adolescence—are consistent with deficient NMDA receptor function in schizophrenia. Cannabinoid CB1 receptor and D2 receptors are localized presynaptically on glutamate terminals and work to inhibit the release of glutamate. Cannabis, therefore, reduces glutamate release, in particular in corticostriatal regions (Gerdeman and Lovinger, 2001), leading to deficient activation of NMDA receptors,

whereas reduced D2 receptor function produces modest increases in glutamate release (Cepeda et al., 2001; Yamamoto and Davy, 1992).

These lines of evidence have led to the current thinking that disruptions in any of the numerous mechanisms that influence the function of NMDA receptors, by either modifying the kinetics of the NMDA channel itself, or the function of proteins that link NMDA receptors to signal transduction pathways, can compromise behavior in a manner suggested by the symptoms of schizophrenia. This theory is consistent with the complex genetic predisposition feature of schizophrenia because it predicts that any of the genes that encode or regulate the large number of proteins that influence the function of NMDA receptors would be plausible susceptibility genes for this disease. It is also consistent with a strong environmental influence on the disease process because, unlike other known brain receptors that are simply activated by ligand binding to the receptor, opening of NMDA receptor channels depends on coinciding membrane potential depolarization and agonist binding. Thus, processing of context related information at network or microcircuit levels may disrupt the timing of this coincidence and lead to deficient activation of NMDA receptors.

In addition to theoretical implications, these findings have been the basis for identification of novel therapeutic targets for treatment of schizophrenia (Moghaddam and Adams, 1998). A recent proof-of-concept clinical trial paper by Eli Lilly shows promising results with one of these compounds (Patil et al., 2007). This double-blind placebo-controlled study showed that after four weeks of treatment, an agonist for the metabotropic glutamate 2/3 receptor (mGlu2/3R) has similar efficacy as olanzapine in ameliorating positive and negative symptoms of schizophrenia. At both practical and conceptual levels, these findings have the potential of revolutionizing the field. At a practical level, this may represent the first time where purposeful design and laboratory-based basic and clinical research have led to the discovery of a truly novel target with clinical efficacy for a major psychiatric disorder. At a conceptual level, the results of this clinical trial will compel the field to reevaluate its older theories on schizophrenia and the notion that "all known antipsychotic drugs block dopamine receptors." The trial, of course, must be replicated. Meanwhile, there is great optimism that this proof-of-concept study is finally eliciting a paradigm shift in the field of schizophrenia.

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