Cellular and Molecular Neurobiology, Vol. 26, Nos. 4–6, July/August 2006 (© 2006)
DOI: 10.1007/s10571-006-9062-8

Glutamate and Schizophrenia: Beyond the Dopamine Hypothesis

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Received February 8, 2006; accepted March 15, 2006; Published online: June 14, 2006

SUMMARY

1. After 50 years of antipsychotic drug development focused on the dopamine D2 receptor, schizophrenia remains a chronic, disabling disorder for most affected individuals.

2. Studies over the last decade demonstrate that administration of low doses of NMDA receptor antagonists can cause in normal subjects the negative symptoms, cognitive impairments and physiologic disturbances observed in schizophrenia.

3. Furthermore, a number of recently identified risk genes for schizophrenia affect NMDA receptor function or glutamatergic neurotransmission.

4. Placebo-controlled trials with agents that directly or indirectly activate the glycine modulatory site on the NMDA receptor have shown reduction in negative symptoms, improvement in cognition and in some cases reduction in positive symptoms in schizophrenic patients receiving concurrent antipsychotic medications.

5. Thus, hypofunction of the NMDA receptor, possibly on critical GABAergic interneurons, may contribute to the pathophysiology of schizophrenia.

KEY WORDS: schizophrenia; dopamine; glutamate; D-serine; glycine; negative symptoms; D-amino acid oxidase.

INTRODUCTION

In spite of 50 years of refinement of antipsychotic medications to treat schizophrenia, the disorder remains a very disabling illness. All current antipsychotics exert their effects primarily by blocking D2 dopamine receptors (Snyder, 1981; Seeman, 2002). Existing drugs are poorly tolerated and exhibit little differences in efficacy (Lieberman *et al.*, 2005). However, with the possible exception of clozapine in a subgroup of patients (Meltzer, 1997; Davis *et al.*, 2003), the typical and second generation antipsychotics leave most patients substantially disabled due to negative symptoms and cognitive impairments. The severity of these less responsive symptoms correlates with the atrophic changes in the brain (Kirkpatrick *et al.*, 2001). These persistent symptoms compromise the ability of schizophrenic patients to respond to rehabilitative interventions, to live independently and to gain meaningful

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employment (Evans *et al.*, 2004). Thus, with current treatments, schizophrenia, which affects less than one percent of the population, is the seventh most costly medical illness.

Clearly, the most important challenge for schizophrenia research at the present time is to understand the components of the disorder that are resistant to current treatments. These symptoms likely involve neurotransmitter systems besides dopamine. There is now strong reason to suspect abnormalities in NMDA receptor (NMDAR) function may contribute to these symptoms that are resistant to antipsychotic medications. This assertion should not be considered as contradictory to the dopamine hypothesis because results thus far point to important interactions between dopamine receptors and NMDAR in critical brain regions such as the hippocampus (Lisman and Otmakhova, 2001) and between glutamatergic afferents and subcortical dopaminergic nuclei (Lisman and Grace, 2005).

Etiology of Schizophrenia

The evidence from genetic, brain imaging, clinical and pharmacologic studies indicates that schizophrenia is a heterogeneous group of disorders (Kirkpatrick *et al.*, 2001; Harrison and Weinberger, 2004). Thus, it is evident that no single molecular event could be completely explanatory of the pathophysiology of schizophrenia. Accordingly, a fruitful strategy for understanding this disorder would be to define final common pathway(s) that account for the neurophysiologic dysfunction in the several affected brain regions that result in the symptoms of schizophrenia. By analogy, in Alzheimer's Disease, it is now evident that allelic variants/mutations of several different genes including APP, presenilin I and II, ApoE IV, alpha-anti-chymotrypsin and environmental factors, (education, head trauma, antioxidant exposure) interact to result in the neuropathology (deposition of the Aβ peptide in senile plaques), the selective neuronal vulnerability and the symptomatic manifestations of the disorder (Coyle, 1998). As described later, an attactive common pathway that can contribute to negative symptoms and cognitive impairments in schizophrenia causes hypofunction of NMDAR. This may occur through several different mechanisms, e.g., by reduced the availability of the NMDAR co-agonist, D-serine, by increased concentration of NMDAR glycine modulatory site antagonists and by reduced glutamate release.

The Glutamatergic Synapse

The glutamatergic synapse consists of a tight functional relationship among the presynaptic terminal, the postsynaptic spine and the ensheathing astrocyte end-foot (Araque *et al.*, 1999; Coyle *et al.*, 2002). Synaptic glutamate is synthesized from glutamine supplied by the astrocyte, packaged into vesicles and released during action potentials. The presynaptic terminals of pyramidal cells in the primate cortex and limbic system also have high concentrations of

N-acetyl-aspartyl glutamate (NAAG), which is co-localized and released with glutamate (Passani *et al.*, 1997; Bergeron *et al.*, 2005), and which modulates glutamatergic neurotransmission. The postsynaptic effects of glutamate are mediated by three families of glutamate-gated ion channels: the AMPA, kainate and NMDA receptors. The AMPA receptors play the primary role in the generation of the excitatory postsynaptic currents (EPSCs) responsible for triggering action potentials. NMDAR have a critical role in synaptic plasticity, but can also contribute to the EPSCs and dendritic spikes. In addition, G-protein coupled glutamate receptors, the metabotropic receptors, modulate glutamatergic neurotransmission; for instance, presynaptic mGluR3 receptors inhibit the release of glutamate (Xi *et al.*, 2002).

The NMDA receptor is a tetramer containing two subunits; NR1, which is required for channel function, and NR2A-D, which affect the biophysical and pharmacologic characteristics of the NMDAR (Lynch and Guttmann, 2001). At resting membrane potential, the NMDAR channel is blocked by Mg^{2+}, a block that can be removed with depolarization. Within the channel is a binding site for dissociative anaesthetics (e.g., ketamine, MK-801), which act as use-dependent, non-competitive antagonists. Aside from the glutamate/NMDA recognition site, a second site on NR1 binds glycine/D-serine (this is termed the *glycine modulatory site*, GMS; also, the *Glycine B Receptor*) and must be occupied for glutamate to open the channel (Berger *et al.*, 1998). The open NMDAR allows the influx of Ca^{2+}, which activates a cascade of enzymes that affect the biochemistry of local synaptic plasticity and the processes of gene expression (Hong *et al.*, 2004). During the induction of long-term potentiation (LTP), convergent excitatory synapses cause robust synaptic de-polarization, Ca^{2+} entry through NMDAR and persistent upregulation of AMPAR function (Malenka, 2003). More prolonged activation of NMDAR can cause spine proliferation as well as have trophic effects on postsynaptic neurons (Llado *et al.*, 1999). Thus, the NMDAR is viewed as central to the mechanisms of synaptic plasticity (Liu *et al.*, 2004). Conversely, excessive activation of extra-synaptic NMDAR can result in oxidative stress and neuronal death (excitotoxicity) (Coyle *et al.*, 2002).

The astrocyte is an important participant in glutamatergic neurotransmission (Schousboe, 2003). Aside from providing lactate for oxidative metabolism and glutamine for glutamate synthesis at the glutamatergic terminal, the astrocyte plays a central role in regulating NMDAR function. The two glutamate transporters responsible for inactivating synaptic glutamate and protecting against excitotoxicity, EAAT1 and 2, are expressed by the astrocytes (Schluter *et al.*, 2002). The glycine transporter1 (GlyT1), which regulates synaptic glycine, is astrocytic (Zafra *et al.*, 1995). Both serine racemase, that synthesizes D-serine (SR), and D-amino acid oxidase (DAAO), which catabolizes D-serine, are localized to astrocytes (Schell, 2004; Wolosker *et al.*, 1999; Kirkpatrick *et al.*, 2001; Harrison and Weinberger, 2004). GCPII, which degrades NAAG, is concentrated in the astrocyte end-feet (Berger *et al.*, 1999). NAAG activates presynaptic mGluR3 (Wroblewska *et al.*, 1997), which downregulates glutamate release. Interestingly, it has become apparent that astrocytes exhibit marked regional differences in the expression of these NMDAR modulatory processes.

NMDAR Hypofunction and Schizophrenia

The NMDA receptor hypofunction hypothesis for schizophrenia receives support from five separate types of investigation: NMDAR antagonist studies, brain imaging studies, genetic studies, postmortem studies and pharmacologic interventions that enhance NMDAR function in subjects with schizophrenia. In fact, the results from the genetic studies over the last 5 years in the context of the four other types of evidence make a more compelling case for the role of glutamate/NMDAR in the endophenotype of schizophrenia than dopamine. And some evidence supports the notion that psychosis, which is not unique to schizophrenia, is secondary to NMDAR hypofunction (Kegeles *et al.*, 2000). The following section will review these findings.

NMDAR Challenge Studies

Since their introduction nearly 50 years ago, the dissociative anaesthetics such as ketamine and phencyclidine (PCP) were known to cause a psychotic syndrome that was difficult to distinguish from schizophrenia (Luby *et al.*, 1959; Itil *et al.*, 1967). Notably, children are relatively resistant to this side-effect, mirroring the developmental trajectory for psychosis in schizophrenia (Reich and Silvay, 1989). Based upon the emerging pharmacology of the NMDAR, Javitt and Zukin (1991) proposed that the psychotomimetic effects of PCP were due to blockade of the NMDA receptors. Given that PCP abusers may be at high risk for psychopathology, their inference that NMDAR blockade might cause the symptoms of schizophrenia met with some resistance.

Krystal *et al.* (1994) advanced the hypothesis substantially when they demonstrated that normal volunteers receiving steady low dose infusion of ketamine exhibited negative symptoms and subtle cognitive impairments reminiscent of schizophrenia and partial manifestation of positive symptoms such as illusions. An important but often overlooked aspect of the study is that the subjects were not "delirious" since they had normal Mini-Mental Status Exams (MMSE), suggesting that a subpopulation of sensitive NMDAR were affected by the low dose of ketamine. Lahti *et al.* (2001) demonstrated that subjects with remitted schizophrenia were quite sensitive to the psychotomimetic effects of infused ketamine and that it brought forward symptoms that were unique to the individual. Newcomer *et al.* (1999) extended the findings of Krystal *et al.* (1994) by showing that declarative memory, the form impaired in schizophrenia, was quite sensitive to low dose ketamine infusion. Adler *et al.* (1999) using similar methods found that ketamine induced a thought disorder similar to that observed in schizophrenia. These studies suggested that ketamine more faithfully replicated the negative symptoms and the cognitive symptoms of schizophrenia, which represent the endophenotype, than the positive symptoms.

The ketamine challenge strategy has also been shown to reproduce in normals several of the physiologic signs of schizophrenia. For example, there is an increased prevalence of eye tracking abnormalities in subjects with schizophrenia and their first-degree relatives (Holzman *et al.*, 1988). Low dose ketamine mimics in controls the abnormal saccades observed in schizophrenia (Radant *et al.*, 1998).

Schizophrenic subjects exhibit enhanced release of forebrain dopamine with an amphetamine challenge as measured by ^{125}I-IBZM displacement with PET scanning; low dose ketamine produces the same effect in normal volunteers (Kegeles *et al.* 2000).

Event related brain potentials (ERP), in which the EEG is recorded during the presentation of a sensory stimulus (auditory, visual), has proved to be a powerful strategy for measuring neuronal processing in schizophrenic subjects as compared to controls and therefore a way of probing NMDAR function. A number of paradigms have been exploited with clear evidence of differences in the P50 (50 ms) and the P300 (300 ms) waves between schizophrenic subjects and controls. For example, Thoma *et al.* (2005) showed a correlation between event related field at 50 ms in the right hemisphere and negative symptoms. Smaller P 300 waves induced by auditory or visual stimuli correlated with duration of illness (van der Stelt *et al.*, 2005). Javitt has demonstrated that schizophrenic subjects have ERP abnormalities not only at cognitive levels but also at perceptual levels (Butler *et al.*, 2005). He and his colleagues have found markedly reduced response to magnocellular biased but not parvocellular biased visual stimuli, similar to the effects of local infusion of ketamine into the lateral geniculate nucleus of the cat. Furthermore, his research in monkeys indicates the central role of NMDAR in mismatch negativity paradigms for ERPs (Javitt *et al.*, 1994, 1996). These findings have been confirmed in normal human subjects with low dose ketamine producing impairments similar to those observed in subjects with schizophrenia (Umbrecht *et al.*, 2000).

Neuropathology

Benes pioneered the investigation of the cellular pathology of corticolimbic GABAergic inter-neurons in schizophrenia (Benes *et al.*, 1991). Since then, a remarkably reproducible series of findings based on neurochemical, immunocytochemical, in situ hybridization and DNA chip array methods, have confirmed the reduction in the presynaptic markers for GABAergic inter-neurons in subsectors of the hippocampal formation and in the intermediate layers of the prefrontal and cingulate cortex [for reviews, (Benes and Berretta, 2001; Lewis *et al.*, 2004)]. These findings include reduced expression of GAD67, the GABA transporter, GAT, and the co-expressed calcium binding protein, parvalbumin. Lewis and colleagues have presented evidence for the loss of GABAergic chandelier cell terminals ("cartridges") on pyramidal initial axon segments (Woo *et al.*, 1998; Volk *et al.*, 2001). That these distributed but selective reductions in GABAergic markers have functional significance is supported by the evidence from ligand binding and $GABA_A$ receptor subunit expression studies. These studies show compensatory upregulation of postsynaptic $GABA_A$ receptors in the very regions associated with downregulation of presynaptic GABAergic markers (Hanada *et al.*, 1987; Benes *et al.*, 1996; Impagnatiello *et al.*, 1998; Volk *et al.*, 2002). Yurgelun-Todd *et al.* (2005) have found evidence supporting these postmortem findings with in vivo MRS, which revealed a significant reduction in GABA levels in the prefrontal cortex in schizophrenia.

Recent evidence suggests that the reduced GABAergic function in schizophrenia may result from NMDAR hypofunction. In electrophysiologic studies, the

GABAergic inter-neurons in the CA1 region of the hippocampus were shown to be 10-fold more sensitive to the inhibitory effects of amino-phosphono-valeric acid (APV) and NAAG than adjacent pyramidal cells (Grunze *et al.*, 1996). Li *et al.* (2002) have shown that limbic GABAergic inter-neurons are more sensitive to the dissociative anaesthetic MK801 than the adjacent the pyramidal neurons. Paulson *et al.* (2003) reported that chronic treatment with MK801 resulted in downregulation in the expression of GAD and GAT in the frontal cortex of rats similar to the reductions observed in schizophrenia. Furthermore, preclinical studies in rats have shown how disinhibition of the glutamatergic input from the basolateral nucleus of the amygdala to the hippocampus affects GABAergic indices and receptor expression in the hippocampus in a manner virtually identical to the postmortem findings in schizophrenia (Berretta *et al.*, 2004; Gisabella *et al.*, 2005).

Importantly, the association of NMDAR hypofunction and GABAergic interneurons was further strengthened with the postmortem findings from a dual in situ hybridization study that showed a reduced number of GAD67 expressing neurons that co-express NR2A in the prefrontal cortex in schizophrenics as compared to controls (Woo *et al.*, 2004). Thus, the well-replicated GABAergic deficits in schizophrenia, for which there is little genetic evidence of their being a primary defect, may be a direct consequence of NMDAR hypofunction. Futhermore, computational models indicate that the loss of the NMDAR component of the EPSC on hippocampal GABAergic neurons would disrupt memory and cognitive processing in a manner analogous to that found in schizophrenia (Grunze *et al.*, 1996).

Mounting evidence, especially from postmortem studies, points to endogenous NMDAR antagonists as contributors to NMDAR hypofunction. One of the initial postmortem findings that prompted our interest in the role of glutamate in schizophrenia was the demonstration that the activity of glutamate carboxypeptidase II (GCPII), which catabolyzes NAAG to NAA and glutamate, was reduced in frontal cortex, hippocampus and temporal cortex in a postmortem comparison of schizophrenic subjects to suitable controls (Tsai *et al.*, 1995). NAAG is a potent and specific agonist at the mGluR3 receptor (Wroblewska *et al.*, 1997; Bischofberger and Schild, 1996), which gene has been associated with the risk for schizophrenia (Egan *et al.*, 2004). And NAAG is a glycine reversible antagonist of the NMDAR (Grunze *et al.*, 1996; Bergeron *et al.*, 2005). Subsequent studies by others utilizing DNA chip array in the analysis of frontal cortex in geriatric schizophrenic subjects (Hakak *et al.*, 2001) and a quantitative PCR study of the Stanley collection have confirmed the robust reduction in the expression of GCPII in prefrontal cortex in schizophrenia (Huffacker *et al.*, 2003).

Another endogenous GMS antagonist, kynurenic acid, has been shown to be elevated in prefrontal cortex but not motor cortex in postmortem studies of schizophrenia (Schwarcz *et al.*, 2001). Kynurenic acid levels are also elevated in the CSF of living patients with schizophrenia (Erhardt *et al.*, 2001; Nilsson *et al.*, 2005). Furthermore, tryptophan-2, 3-dioxygenase, an upstream enzyme in kynurenic acid synthesis pathway, is also upregulated in the frontal cortex in schizophrenic subjects (Miller *et al.*, 2004). Erhardt *et al.* (2004) have shown that elevation of endogenous brain kynurenic acid in rats disrupts the prepulse inhibition of the acoustic startle

reflex, a sensory gating abnormality common in schizophrenia, and that this disruption can be reversed by treatment with clozapine.

Imaging Studies

As noted above, structural brain imaging studies over the last two decades have provided compelling evidence that schizophrenia is associated with enlargement of the lateral ventricles and the loss of volume in the prefrontal cortex, the temporal cortex, the hippocampus, the amygdala and the thalamus (Heckers, 2001; Yamasue *et al.*, 2004). Prospective studies indicate that reduced cortical volume is present at first episode but can progress during the first several years of illness (DeLisi *et al.*, 2004; Gogtay *et al.*, 2004; Mittelman *et al.*, 2003). MRS studies have repeatedly revealed slight but significant reductions in the levels of NAA in prefrontal cortex (Sigmundsson *et al.*, 2003), temporal lobe (Deicken *et al.*, 1999) and thalamus (Auer *et al.*, 2001). Immunocytochemical studies have demonstated that NAA is particularly enriched in the projecting glutamatergic neurons in these regions (Simmons *et al.*, 1991). As there is little indication of neuronal degeneration in these regions, these results suggest compromised glutamatergic function (Selemon *et al.*, 2003). Furthermore, methods to assess the organization of axonal projections such as diffusion tensor imaging point to a disruption in terminal fields in the prefrontal cortex in schizophrenia (Davis *et al.*, 2003). Weinberger and colleagues have argued that such evidence supports the notion of "disconnection" in schizophrenia, which would affect primarily glutamatergic afferents (Meyer-Lindenberg *et al.*, 2001).

Functional imaging studies have greatly assisted the interpretation of the subtle but disabling cognitive impairments in schizophrenia. Weinberger's pioneering use of the Wisconsin Card Sort Task, which schizophrenic subjects perform poorly, in functional brain imaging studies dramatically enhanced the evidence of hypofrontality in schizophrenic subjects as compared to controls (Berman *et al.*, 1986). In PET studies, Heckers *et al.* (1998) were able to dissociate activations in the dorsolateral prefrontal cortex and the hippocampus during verbal episodic memory retrieval in schizophrenics (Heckers *et al.*, 1998). Hippocampal activation was attenuated during conscious recollection of study words in the schizophrenic subjects; moreover, basal activity appeared to be elevated, resulting in a ceiling effect. Heckers *et al.* (1999) showed that on the performance of memory task, schizophrenics with deficit syndrome exhibited less activation of the frontal cortex than those without deficit syndrome although there was no difference between the two with regard to hippocampal activation. Schizophrenia is associated with attenuated right thalamic and right prefrontal cortex activation during the recognition of novel visual stimuli.

Genetics

There is a consensus that schizophrenia is a disorder with a high degree of heritability (0.8) (Harrison and Owen, 2003). However, it does not appear to be a disorder of Mendellian genetics but rather of complex genetics, in which multiple genes of small effect interact to cause the phenotype (Kirov *et al.*, 2005). Environmental (primarily, perinatal insults) or epigenetic factors contribute to the phenotype

(Zornberg *et al.*, 2000). In a recent critical review of the status of genetic studies in schizophrenia, Harrison and Weinberger (2004) identified seven plausible risk genes for schizophrenia based upon linkage and association studies. These include COMT (Goldberg *et al.*, 2003), Dysbindin (Blake *et al.*, 1998), Neuregulin (Falls, 2003), Regulator of G-protein Signaling 4 (RGS4; Williams *et al.*, 2004), Disrupted In Schizophrenia 1 (DISC1; Cannon *et al.*, 2005), metabotrophic glutamate receptor-3 (GRM3; Egan *et al.*, 2004) and G-72 (Chumakov *et al.*, 2002). D-Amino acid oxidase (DAAO) and proline oxidase (Liu *et al.*, 2002), both of which also affect glutamatergic neurotransmission, have also received support as candidate risk genes for schizophrenia (Kirov *et al.*, 2005)

G72, a gene of recent evolutionary appearance, encodes a protein that activates DAAO, the enzyme that catabolizes D-serine (Chumakov *et al.*, 2002). DAAO appears to be the critcal determinant of D-serine levels as its activity correlates inversely with D-serine levels both regionally and developmently (Hashimoto, 2002). Reduced availability of D-serine would lead to NMDAR hypofunction (Stevens *et al.*, 2003). Over the last 3 years, seven studies have demonstrated an association of G72 with the risk for schizophrenia and two with the risk for bipolar disorder (Chumakov *et al.*, 2002; Hattori *et al.*, 2003; Addington *et al.*, 2004; Chen *et al.*, 2004; Korostishevsky *et al.*, 2004; Schumacher *et al.*, 2004; Wang *et al.*, 2004; Korostishevsky *et al.*, 2006), One study reported increased expression of G72 in prefrontal cortex (Hattori *et al.*, 2003). The impressive replications of the association of G72 with the risk for schizophrenia is all the more intriguing, given recently replicated findings that: (1) D-serine reduces negative symptoms, improves cognition and reduces positive symptoms in patients with chronic schizophrenia, who are receiving concurrent typical antipsychotic medications (Tsai *et al.*, 1998; Heresco-Levy *et al.*, 2002) and (2) that serum and CSF levels of D-serine are reduced in schizophrenic subjects (Hashimoto *et al.*, 2003, 2005).

GRM3: Similarly, there is a connection of GRM3 to glutamatergic neurotransmission. GRM3 encodes for mGluR3 at which *N*-acetyl-aspartyl glutamate (NAAG) is a potent and specific agonist (Wroblewska *et al.*, 1997). mGluR3 down regulates the release of glutamate and thereby would cause NMDAR hypofunction. Our research suggests that the mGluR3 agonist NAAG may be increased in cortico-limbic regions in schizophrenia due to downregulation of its catabolic enzyme, GCPII (Tsai *et al.*, 1995; Hakak *et al.*, 2001, Huffacker *et al.*, 2003)

DTNP1: Dysbindin (DTNP1; 6p24-22) has emerged as one of the most promising candidate genes for schizophrenia (Williams *et al.*, 2004). Dysbindin is concentrated the presynaptic glutamatergic terminals where it interacts with SNAP and synapsin 1 and modulates vesicular release of glutamate (Numakawa *et al.*, 2004). The expression of dysbindin is reduced in prefrontal cortex and hippocampus in schizophrenia (Talbot *et al.*, 2004; Weickert *et al.*, 2004). Notably, the dysbindin genotype has been associated with general cognitive ability and poor premorbid function in schizophrenia (Burdick *et al.*, in press; Gornick *et al.*, in press).

NRG1: The association of the neuregulin gene with the risk for schizophrenia is also particularly robust (Petryshen *et al.*, 2005). Neuregulin is a component of

the Erb signalling pathway, and mice with a null mutation of its gene express lower levels of NR1 (Falls, 2003). Furthermore, neuregulin directly reduces NMDAR currents in cultured prefrontal cortical neurons (Gu *et al.*, 2005).

GMS as a Potential Drug Target

Because direct activation of the NMDAR could lead to excitotoxicity and neuronal degeneration, an indirect strategy to enhance NMDAR function would be to pharmacologically activate the GMS on the NMDAR. This would not tonically activate NMDAR but would enhance NMDAR response to phasically released glutamate. Preclinical studies in rat indicated that high doses of the full GMS agonist, glycine, reversed the behavioral effects of NMDR antagonists (Javitt *et al.*, 1999). The GMS partial agonist, D-cycloserine, with acute administration enhanced performance of memory tasks in rats (Land and Riccio, 1999; Andersen *et al.*, 2002). However, the suitability of the GMS strategy had been questioned because the concentration of glycine in the CSF was at least ten-fold greater than the K_D of glycine for the GMS, suggesting that the GMS was saturated by endogenous agonists.

Guastella *et al.* (1992) cloned Na^+ dependent glycine transporter (GlyT1) from brain and demonstrated that it was inhibited by sarcosine. In situ hybridizaton revealed its localization to glia with an uneven regional brain distribution and high expression in brainstem and cerebellum. We took advantage of sarcosine analogue (NFPS) with its sub-nanomolar affinity for GlyT1 to study the impact of inhibiting GlyT1 on glutamatergic neurotransnmission in the CA1 sector of the acute hippocampal slice preparation (Bergeron *et al.*, 1998). Perfusion of the slice with 1 or 10 μM glycine had little effect on the NMDAR component of the EPS but the addition of NFPS caused a robust increase in the NMDAR currents. Chen *et al.* (2003) showed similar effects of NFPS on NMDAR currents in the acute frontal cortex slice. Kinney *et al.* (2003) have extended the studies in vivo, demonstrating not only increased NMDAR currents in the dentate gyrus after systemic treatment with NFPS but also increased LTP. Thus, the GMS is not saturated by endogenous agonists and is a suitable target for directly or indirectly acting agonists.

Studies of mice with a null mutation of GlyT1 add credence to the hypothesis that NMDAR hypofunction could be mediated through the GMS (Tsai *et al.*, 2004). Although GlyT1 $-/-$ die soon after birth, it is not because of NMDAR related toxicity but rather because of respiratory failure due to excessive stimulation of brainstem inhibitory glycine receptors (Gomeza *et al.*, 2003). GlyT1 $+/-$ do not differ from wild type (WT) litter mates in spontaneous activity but exhibited a nearly fourfold persistence of the memory of the platform's location in the Morris water maze (Tsai *et al.*, 2004). Furthermore, the GlyT1 $+/-$ were more resistant to the disruptive effect of D-amphetamine that WT litter mates, a model psychotic vulnerability. Thus, mice with persistently enhanced GMS function in the GlyT1 $+/-$ suggest a phenotype that is the mirror image of a schizophrenia phenotype-improved memory and resistance to amphetamine.

Pharmacologic Studies on Schizophrenia

If hypofunction of NMDAR contributes to the pathophysiology of schizophrenia, then a logical prediction is that agents that enhance NMDAR function should reduce symptoms of the disorder, especially those associated with the endophenotype such as cognitive impairment and negative symptoms. To avoid the potential for excitotoxicity, the strategy that has been exploited was to give agents that act at the GMS on NMDAR. Goff *et al.* (1995) used the partial GMS agonist, D-cycloserine, which crosses the blood brain barrier, in an initial dose finding study and observed a U-shaped dose response curve with improvement in negative symptoms and reduction in cognitive impairments at a dose of 50 mg/day. In a large parallel placebo-controlled trial, Goff *et al.* (1999) replicated the effects of D-cycloserine on negative symptoms in chronic schizophrenics receiving typical antipsychotics but not the cognitive effects (Goff *et al.*, 1999). Furthermore, functional brain imaging studies now provide evidence that D-cycloserine enhances left superior temporal gyrus activation in schizophrenic subjects performing a memory task and that the response correlates significantly with the reduction in negative symptoms (Yurgelun-Todd *et al.*, 2005). On the negative side, Goff *et al.* (2005) recently reported that in a 6-month trial 50 mg/day of D-cycloserine did not separate from placebo in any primary out-come measures including negative symptoms.

Leiderman *et al.* (1996) used high dose (30–60 g/day) glycine and showed significant improvement in negative symptoms and cognitive impairments in chronic schizophrenic subjects receiving concurrent typical antipsychotics. The findings with the full agonist glycine have been replicated in two additional clinical trials (Heresco-Levy *et al.*, 1999; Javitt *et al.*, 2001). However, the multi-center CONSIST study (Buchanen *et al.*, 2005), which compared both D-cycloserine and glycine to placebo in patients with chronic schizophrenia, found no significant differences between the drugs and placebo on any out-come measures including negative symptoms.

The reasons for the disparities in the results from these studies are unclear. D-cycloserine is not the optimal agent for testing the GMS strategy because it is a partial agonist with 50% of the efficacy of glycine (Watson *et al.*, 1990). Furthermore, it causes NMDAR desensitization with chronic administration and loss of cognitive enhancing effects in rodent studies (Quartermain *et al.*, 1994). Indeed, robust and persistent cognitive changes have been reported when CBT was coupled with just a single dose of D-cycloserine (Ressler *et al.*, 2004). With regard to the negative findings with glycine in the CONSIST study, Javitt (personal communication) points out that serum levels of glycine were 50% lower than in the positive studies and that significant site differences were noted.

Of the GMS agonists, D-serine would appear to be the best candidate for enhancing NMDAR function. D-serine crosses the blood-brain barrier three times better than glycine (Oldendorf, 1971), has a threefold greater potency at NMDAR than glycine (Matsui *et al.*, 1995) and exhibits a long half-life in cortex upon peripheral administration (Hashimoto and Chiba, 2004). Tsai *et al.* (1998) examined the effects of D-serine in chronic schizophrenic patients receiving typical antipsychotic in a placebo-controlled trial and found reduction in negative symptoms,

improvement in cognition as assessed by the Wisconsin Card Sort Test (WCST) and reduction in positive symptoms. This effect on all three symptom domains by D-serine has been replicated in a placebo-controlled trial in chronic schizophrenic subjects receiving concurrent antipsychotics carried out in Israel (Heresco-Levy *et al.*, 2002). Tsai *et al.* (2004) examined the effects of sarcosine, the endogenous inhibitor of GlyT1, in chronic schizophrenic patients and found that it reduced negative symptoms, improved cognition and reduced positive symptoms in a placebo-controlled trial in chronic schizophrenics receiving concurrent antipsychotics. Furthermore, sarcosine appeared to be more effective in the acutely symptomatic patients (Lane *et al.*, 2005). What D-cycloserine, glycine, D-serine and sarcosine have in common is that they all directly or indirectly enhance GMS function on the NMDAR.

Clozapine

Of all antipsychotics, clozapine has been shown to have rather remarkable and unique effects on a subpopulation of schizophrenic patients that respond poorly to other antipsychotics (Meltzer and McGurk, 1999). In addition, clozapine treatment has been associated with reduction in the rate of suicide, reduction in smoking and reduction in abuse of other substances in schizophrenic patients (Drake *et al.*, 2000; Meltzer *et al.*, 2003; Zimmet *et al.*, 2000). The explanation for these effects of clozapine has remained illusive. However, Goff and his collaborators carried out two independent studies with D-cycloserine in clozapine responders and observed a significant exacerbation of negative symptoms (Goff *et al.*, 1996; Goff *et al.*, 1999). Furthermore, they showed that the addition of the full agonist, glycine, (Evins *et al.*, 2000) had no effects on negative symptoms in clozapine responders. And Tsai *et al.* (1999) showed that the addition of the full agonist D-serine to clozapine responders also had no effect on negative symptoms. These findings suggest that clozapine may exert its effects on negative symptoms by causing full occupancy of the GMS. Full occupancy of the GMS with clozapine would cause the partial agonist, D-cycloserine, to behave like an antagonist thereby exacerbating negative symptoms and the full agonists, glycine and D-serine, to lack efficacy (Coyle and Tsai, 2004).

Enhanced NMDAR function with chronic clozapine treatment has been demonstrated in rat frontal cortex (Ninan *et al.*, 2003). Javitt *et al.* (2005) has proposed that the effects of clozapine on negative symptoms results from inhibition of a novel glycine transporter. Regardless of the mechanism, these findings further support the conclusion that enhancement of NMDAR function addresses symptoms in schizophrenia that are poorly responsive to typical antipsychotics and atypical psychotics aside from clozapines.

Because of the limitations of a partial agonist (desensitization, inconsistent clinical results), we believe that the proposed studies on the more potent and efficacious full agonist, D-serine, will provide a better vehicle to test of our hypothesis in schizophrenic patients and permit a more confident movement from genetic and hippocampal lesion models in mice to the human situation.

CONCLUSION

The accretion of evidence in support of the hypothesis that hypofunction of NMDA receptors contributes to the symptoms of schizophrenia, especially the endophenotype, over the last decade, has provided the first compelling alternative to the dopamine hypothesis. Findings from small to modest sized placebo control trials suggest that enhancing NMDAR function via the GMS consistently affects negative symptoms and to a varying degree cognitive symptoms, the domains of the disorder most resistant to dopamine D2 receptor directed therapy.

Enhanced NMDAR function may have benefits that could be more profound than simply acute effects on symptoms observed in the relatively brief clinical trials. Cortical atrophy (Kuperberg *et al.*, 2003) and loss of dendritic spines (Hill *et al.*, in press) observed in schizophrenia may be predictable consequences of the persistent loss of the trophic effects of NMDAR activity. The therapeutic effects of clozapine on negative symptoms in responsive patients can evolve over months (Meltzer, 1997), suggesting that the effects reflect a gradual reparative process for this antipsychotic that may have unique effects on NMDAR. The neurotrophic and neuroplastic promoting effects of agents acting via the GMS could potentiate cognitive rehabilitation, which has had limited success with current antipsychotics. The recent demonstration that D-cycloserine robustly and persistently potentiates the effects of cognitive–behavioral therapy (Ressler *et al.*, 2004) lends support to this inference. As our knowledge of risk genes becomes more certain, genomic studies could assist in identifying youth with high vulnerability to schizophrenia. Early intervention with drugs that enhance NMDAR may offer the opportunity for preventive interventions to reverse the insidious processes of neuronal atrophy and disconnection that appear to be the neuropathologic core of schizophrenia.

Comment

Finally, it is only fitting that the lessons learned from Julie Axelrod during my time as a postdoctoral fellow (1970–73) be acknowledged. He recommended pursuing lines of research that are not in the main stream in order to develop novel insights ("Be the firstest with the mostest"). We focused on glutamatergic signal transduction before there was any evidence that it could be relevant to neuropsychiatric disorders (Coyle and Schwarcz, 1976). He counseled us to follow the results, especially if they lead in unexpected directions. Two decades of research on *N*-acetyl aspartyl glutamate has illuminated the negative modulation of glutamatergic neurotransmission and the unexpected central role of glia in NMDAR function (Coyle and Schwarcz, 2000). He supported following your "gut" instincts. Thus, we demonstrated the robust effects of D-serine on the symptoms of schizophrenia (Tsai *et al.*, 1998) 4 years before the first genetic evidence that it may be an important risk pathway for schizophrenia appeared (Chumakov *et al.*, 2002). Finally, Julie Axelrod demonstrated how to be a translational researcher before the term was conceived. Our basic research has always been guided with an eye toward what it may tell us about the pathophysiology of neuropsychiatric disorders.

ACKNOWLEDGMENTS

Some of the research described in this review was supported by a National Institute of Mental Health Conte Center on the Neurobiology of Schizophrenia (MH P50-60450) and MH RO1-572901 and a Lieber Senior Investigator Award from the National Alliance for Research on Schizophrenia and Affective Disorder (NARSAD) to JTC.

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