The Emerging Role of Glutamate in the Pathophysiology and Treatment of Schizophrenia

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Objective: Research has implicated dysfunction of glutamatergic neurotransmission in the pathophysiology of schizophrenia. This review evaluates evidence from preclinical and clinical studies that brain glutamatergic neurotransmission is altered in schizophrenia, may affect symptom expression, and is modulated by antipsychotic drugs.

Method: A comprehensive review of scientific articles published over the last decade that address the role of glutamate in the pathophysiology of schizophrenia was carried out.

Results: Glutamatergic neurons are the major excitatory pathways linking the cortex, limbic system, and thalamus, regions that have been implicated in schizophrenia. Postmortem studies have revealed alterations in pre- and postsynaptic markers for glutamatergic neurons in several brain regions in schizophrenia. The *N*-methyl-D-aspartic acid (NMDA) subtype of glutamate receptor may be particularly important as blockade of this receptor by the dissociative anesthetics reproduces in normal subjects the symptomatic manifestations of schizophrenia, including negative symptoms and cognitive impairments, and increases dopamine release in the mesolimbic system. Agents that indirectly enhance NMDA receptor function via the glycine modulatory site reduce negative symptoms and variably improve cognitive functioning in schizophrenic subjects receiving typical antipsychotics.

Conclusions: Dysfunction of glutamatergic neurotransmission may play an important role in the pathophysiology of schizophrenia, especially of the negative symptoms and cognitive impairments associated with the disorder, and is a promising target for drug development.

(Am J Psychiatry 2001; 158:1367–1377)

Because glutamate is ubiquitous in the brain as the primary excitatory neurotransmitter, a model positing generalized abnormalities of glutamatergic activity would be unlikely to account for the clinical characteristics of schizophrenia with any degree of specificity. However, specificity has been observed with pharmacological challenges, where antagonism of the glutamatergic *N*-methyl-D-aspartic acid (NMDA) receptor complex has produced behavioral and cognitive deficits in normal subjects that closely mimic schizophrenia (1), and in therapeutic trials, in which agents that enhance NMDA receptor activity have selectively improved symptoms in schizophrenia patients (2). In addition, postmortem studies have identified abnormalities of glutamate receptor density and subunit composition in the prefrontal cortex, thalamus, and temporal lobe (3–5), areas that exhibit impaired activation during performance of cognitive tasks in schizophrenia (6, 7). These findings suggest that glutamatergic dysregulation may occur in regionally specific subpopulations of glutamatergic receptors and so support the potential value of a glutamatergic model for guiding research into the pathophysiology and treatment of schizophrenia.

Although the relationship is speculative, glutamatergic receptor dysfunction could also play a role in neuroarchitectural abnormalities that have been described in schizophrenia, such as aberrant neuronal migration (8, 9) or reduced synaptic connections (10), because of the role of glutamatergic receptors in regulating neuronal migration, neurite outgrowth, synaptogenesis, and the "pruning" of supernumerary neurons by apoptosis (11–14). Neuronal excitotoxicity mediated by glutamatergic receptors has also been proposed as a consequence of dysregulated glutamatergic transmission in schizophrenia (15), but evidence for neurodegeneration from glutamate toxicity in the brain in schizophrenia remains poorly established. Because an extensive and functionally diverse range of glutamate receptor subtypes are genetically encoded and can interact with environmental stressors during brain development, the model of glutamatergic dysfunction may account for the interplay of genetic and environmental risk factors identified in schizophrenia. Furthermore, a proposed dysfunction of glutamatergic neuronal systems is not inconsistent with the dopamine hypothesis of schizophrenia, since reciprocal synaptic relationships between forebrain dopaminergic projections and glutamatergic systems have been well described (16), and dysregulation of one system by illness or pharmacological interventions would be expected to alter neurotransmission in the other.

This review will briefly summarize glutamate receptor physiology and evaluate the evidence for glutamatergic

dysfunction in schizophrenia, focusing on postmortem findings, pharmacologic models, and clinical trials examining the effects of glutamatergic agents on the symptomatic manifestations of schizophrenia.

Glutamate Receptors

Glutamate and the structurally related acidic amino acid aspartate activate two families of receptors: ionotropic receptors, which gate cation channels, and metabotropic receptors, which are coupled to G-proteins that affect intracellular metabolic processes (17). The ionotropic receptors are designated by the potent glutamate analogues that selectively activate them: the kainate receptor, the α-amino-3-hydroxy-5-methyl-isoxazole-4-proprionic acid (AMPA) receptor, and the NMDA receptor. Electrophysiologic effects of all three ionotropic receptor families are mediated by the opening of cation channels permeable to Na^+ and, in a subtype-specific fashion, to Ca^{2+}, thereby depolarizing or "exciting" the neuron. AMPA and kainate receptors play the primary role in mediating fast excitatory postsynaptic potentials responsible for excitatory neurotransmission.

The NMDA receptor serves a different role. At resting membrane potential, its channel is blocked by Mg^{2+}. Upon depolarization caused by activation of the kainate and/or AMPA receptors, the Mg^{2+} block is removed, permitting glutamate to open the NMDA channel. The channel is permeable not only to Na^+ but also to Ca^{2+}, an important intracellular signaling ion that activates nitric oxide synthetase, among other enzymes (18). The NMDA receptor has a number of modulatory sites that affect its activity. Within the channel, there is a binding site for the dissociative anesthetics such as phencyclidine (PCP, "angel dust") and ketamine, which serve as noncompetitive antagonists (19). There is also a strychnine-insensitive binding site for the co-agonist glycine, which must be occupied in order for glutamate to open the ion channel (20). This site on the NMDA receptor is distinct from the strychnine-sensitive site associated with the inhibitory glycine receptor in the brainstem and spinal cord. Electrophysiologic studies indicate that the glycine modulatory site is not fully occupied under normal conditions (21–23).

Because the NMDA receptor is recruited only during periods of substantial neuronal depolarization, it appears to serve the purpose of a "coincidence" detector. In this way, the NMDA receptor plays a critical role in a major form of use-dependent synaptic plasticity known as long-term potentiation. In long-term potentiation, a brief period of high-intensity excitatory synaptic activity, which markedly depolarizes the neurons and recruits NMDA receptors, results in a subsequent persistent increase in synaptic efficacy. Long-term potentiation has been linked to memory formation (24).

Molecular cloning has revealed a family of eight genes encoding the metabotropic receptors (19). Four genes encode the peptides (GluR1–GluR4) that form the AMPA receptor. The molecular diversity of AMPA receptors is further enhanced by several splice variants, in which mRNA is constructed from different exons (coding regions of genes), resulting in a number of physiologically distinct receptor channels from the same gene, and from posttranscriptional processing of mRNA. Three genes encode the family of kainate receptors (GluR5–GluR7), whereas two additional genes encode polypeptides (KA1 and KA2) that alter the pharmacologic features of the kainate receptors. This rich receptor diversity in theory can account for significant differences in relative activity and potential toxicity of glutamate receptors and might permit selective pharmacologic manipulations of excitatory neurotransmission.

The glutamatergic ionotropic receptors are formed by the aggregation of four or five subunits, which transverse the cell membrane and form the receptor-ion channel complex. The subunits differ in important pharmacodynamic properties, including affinity for glutamate, threshold for channel opening, and permeability to Ca^{2+} ions. For example, the $GluR_2$ subunit reduces calcium permeability of the AMPA-gated channels; this effect is dependent on the posttranscriptional editing of the $GluR_2$ mRNA. AMPA receptors that lack the $GluR_2$ subunit produce channels permeable to Ca^{2+} influx, which promotes excitotoxic neuronal degeneration (25). Subunit composition may also differ according to the functional role of the receptor. For example, hippocampal inhibitory neurons preferentially express NMDA receptor subunits 2C and 2D (NR_{2C} and NR_{2D}), which are more sensitive to activation by glutamate, owing to a lower threshold for Mg^{2+} blockade, and are more sensitive to antagonists (25, 26). Subunit composition may also be modified by exposure to drugs such as alcohol, nicotine, and antipsychotics (27, 28).

Glutamate Markers and Schizophrenia

Kim et al. (29) reported reduced concentrations of glutamate in the CSF of patients with schizophrenia and first proposed that decreased glutamatergic activity may be an etiologic factor in the disorder. This finding was replicated by some (30, 31) but not all subsequent studies (32–34). Tsai et al. (35) examined eight regions in postmortem brains and found lower concentrations of glutamate and aspartate in the prefrontal cortex and a lower concentration of glutamate in the hippocampus of patients with schizophrenia than in comparison subjects. In addition, the concentration of *N*-acetyl-aspartyl glutamate (NAAG), an acidic dipeptide that acts as an antagonist at NMDA receptors (36), was increased in the hippocampus, and the activity of glutamate carboxypeptidase II (GCP II), the enzyme that cleaves NAAG to produce glutamate and *N*-acetyl aspartate (NAA), was selectively reduced in the frontal cortex, temporal cortex, and hippocampus in the schizophrenia brains. It is noteworthy that magnetic reso-

nance spectroscopic studies in schizophrenic subjects have demonstrated significant reduction of NAA levels in these same regions (37). However, the factors that regulate brain NAA levels are complex (38). While these findings suggest diminished activity at glutamatergic receptors in relevant brain regions, it remains uncertain whether this represents a primary vulnerability factor or a compensatory response to a more proximal defect.

Ligand binding studies in postmortem brains from individuals with schizophrenia have revealed consistent increases in kainate receptors in the prefrontal cortex (39, 40) and decreased AMPA and kainate receptor binding in the hippocampus (41, 42) without consistent abnormalities in NMDA receptor density (3, 4). Immunocytochemical analyses have confirmed a decrease in AMPA receptors in the medial temporal lobe, although reductions in the hippocampus were not found in one study (3). Whereas ligands binding to the cation channel of the NMDA receptor complex ("PCP binding site") have not demonstrated consistent alterations in density (3), Ishimaru et al. (43, 44) reported increased binding to the glycine site of the NMDA receptor throughout the primary sensory cortex and related association fields. In addition, the binding of [^{3}H]-D-aspartate, which labels the transporters that remove synaptic glutamate, was increased in the frontal cortex and decreased in the striatum (39, 45).

The cloning of receptor subunits has facilitated the measurement of glutamate receptor expression in the brain. Most consistent has been the finding of a lower level of mRNA encoding AMPA receptor subunits in the hippocampus and parahippocampus of schizophrenia brains than in the brains of comparison subjects (3, 46, 47). In addition, Akbarian et al. (48) found a higher proportion (1% versus 0.1%) of unedited $GluR_2$ mRNA in the prefrontal cortex of patients with schizophrenia and Alzheimer's disease than in normal subjects, suggesting a higher level of permeability of AMPA receptors to calcium, which could increase the potential for neurotoxicity. Although less studied, the measurement of mRNA encoding kainate receptor subunits has demonstrated a similar pattern of lower density in the hippocampus and parahippocampus (3). Although ligand binding studies have generally failed to find altered NMDA receptor density in the brain in schizophrenia, two studies have found evidence of altered subunit composition of NMDA receptors. Akbarian et al. (48) found a relatively higher level of the NR_{2D} subunit in the prefrontal cortex of schizophrenia subjects than in normal subjects and neuroleptic-treated comparison patients, suggesting increased potential responsiveness to glutamate. In contrast, Gao and colleagues (4) recently reported a relative decrease of the NR_1 subunit in the hippocampus of schizophrenia patients. The investigators demonstrated that this finding was unlikely to represent a medication effect since treatment with haloperidol for 6 months produced no effect on NMDA receptor subunit composition in the rat hippocampus (4). NMDA receptors lacking an NR_1 subunit are nonfunctional; the relative lack of the NR_1 subunit in the brain in schizophrenia suggests less than normal pharmacodynamic responsiveness of NMDA receptors in the hippocampus. Mohn and colleagues (49) used recombinant DNA technology to develop transgenic mice expressing only 5% of the normal levels of NR_1; the NMDA receptor-deficient mice exhibited hyperactivity, stereotypies, and social isolation. The hyperactivity and stereotypies were ameliorated by treatment with haloperidol and clozapine, but only clozapine corrected the impairments in social behaviors. Finally, Ibrahim and colleagues (5) recently reported lower levels of mRNA expression for subunits composing NMDA, AMPA, and kainate receptors in the thalamus of schizophrenia patients, and lower levels of binding to the polyamine and glycine binding sites of thalamic NMDA receptors. Differences between schizophrenic and comparison subjects were most prominent in nuclei with reciprocal projections to limbic regions.

Dissociative Anesthetics

It has long been recognized that PCP produces a syndrome in normal individuals that closely resembles schizophrenia (50, 51) and exacerbates symptoms in patients with chronic schizophrenia (50, 52). At subanesthetic doses, PCP binds to a site within the ion channel of the NMDA receptor that blocks the influx of cations, thereby acting as a noncompetitive antagonist (19). After reports linking PCP to protracted psychosis, abuse, and neurotoxicity (for review see reference 53), PCP was abandoned as an anesthetic agent in humans. Ketamine, another cyclohexylamine anesthetic that has approximately a 10-to-50-fold lower affinity for the NMDA receptor, continues to be used as an anesthetic in children. It is interesting to note that psychotic reactions associated with exposure to ketamine are reported to occur less frequently in children than in adults, suggesting the similar age dependence in vulnerability to psychoses associated with NMDA antagonists and onset of schizophrenia.

When infused intravenously to normal subjects, ketamine produces an amotivational state characterized by blunted affect, withdrawal, and psychomotor retardation (54). Psychotic symptoms typically take the form of suspiciousness, disorganization, and visual or auditory illusions. Psychotomimetic and perceptual effects of PCP are diminished under conditions of sensory deprivation, suggesting that processing of sensory information, rather than perception, is disrupted (55). Dissociative symptoms are also prominent. Although dissociative symptoms are not typically associated with schizophrenia, depersonalization may be an important early feature of the schizophrenia prodrome (53). Finally, ketamine produces the characteristic cognitive deficits of schizophrenia, including impaired performance on the Wisconsin Card Sorting Test and on verbal declarative memory, delayed word recall, and verbal

fluency tests, without evidence of global impairment on the Mini-Mental State Examination (54, 56, 57).

When administered to patients with schizophrenia who were stabilized with conventional neuroleptics, ketamine produces delusions, hallucinations, and thought disorder, consistent with the patient's typical pattern of psychotic relapse (58, 59). Cognitive functioning, particularly recall and recognition memory, are further impaired. It is noteworthy that treatment with clozapine but not with haloperidol attenuated ketamine's exacerbation of clinical symptoms (58, 59).

Jentsch and Roth (19) argued that repeated administration of the NMDA receptor antagonists provides a more valid model of schizophrenia than acute administration. Whereas psychotic symptoms resulting from single-dose infusions of ketamine in normal subjects tend to be mild and somewhat inconsistent, prolonged exposure in PCP abusers is associated with severe, persistent psychotic symptoms more typical of schizophrenia (19, 51). However, it is debated whether the experience of chronic abusers is a valid model for PCP effects on the normal brain (60). Acute administration of ketamine in normal subjects increased perfusion in the prefrontal cortex and anterior cingulate (61–64) and decreased hippocampal perfusion (62), whereas chronic PCP abusers displayed classical "hypofrontality" (65, 66). Compared with single-dose administration, chronic treatment with PCP produced in monkeys more perseveration and fewer nonspecific cognitive deficits and caused memory deficits that persisted after PCP was discontinued (67). These memory deficits were prevented by clozapine treatment.

In rodents, acute administration of NMDA receptor antagonists markedly increases the release of dopamine and glutamate in the prefrontal cortex and subcortical structures (68–70). Moghaddam et al. (71) demonstrated in rats that ketamine-induced augmentation of dopamine release in the prefrontal cortex was associated with impaired performance on a memory task sensitive to prefrontal cortical function; these alterations could be ameliorated by treatment with an AMPA/kainic acid receptor antagonist. Using single cell recordings from dopamine neurons of the ventral tegmental area in rats, Svensson et al. (72) demonstrated that NMDA antagonists increase the rate but decrease the variability of neuronal firing, thereby impairing the signal-to-noise ratio. Burst firing was increased in the ventral tegmental area dopamine neurons that projected to limbic regions but was decreased in dopamine neurons that projected to the prefrontal cortex, indicating regional specificity of effects. By using positron emission tomography to monitor the displacement of [^{11}C]raclopride binding in the striatum after acute administration of ketamine in normal volunteers, several groups have demonstrated increased dopamine release of a magnitude comparable to the effects of amphetamine; furthermore, raclopride displacement correlated with severity of psychotic symptoms (73–75). Microdialysis in monkeys further revealed that increased striatal dopamine release was accompanied by increased reuptake, resulting in increased turnover but unchanged extracellular dopamine concentrations (76).

Whereas the acute administration of NMDA receptor antagonists enhances dopamine turnover in the prefrontal cortex, subchronic administration is associated with decreased dopamine turnover in the frontal cortex (67, 77), reflecting potentially persistent, compensatory effects. Jentsch et al. (77) found a reduction of approximately 75% in prefrontal dopamine utilization, as reflected by the ratio of 3,4-dihydroxyphenylacetic acid (DOPAC) to dopamine in brain tissue after daily administration of 10 mg/kg of PCP in rats for 7 days. Jentsch et al. (78) also demonstrated a 40% reduction in extracellular dopamine by in vivo microdialysis in conscious rats after administration of 5 mg/kg of PCP twice daily for 7 days. In contrast, Lindefors et al. (79) reported that daily administration of 25 mg/kg of ketamine for 7 days increased prefrontal dopamine concentrations without altering concentrations of dopamine metabolites. The explanation for the conflicting results obtained with subchronic ketamine versus phencyclidine administration is not clear but may reflect the shorter half-life of ketamine (19). It is interesting to note that chronic administration of NMDA receptor antagonists results in decreased expression of the dopamine D_1 receptor mRNA in the prefrontal cortex of rats and monkeys (19, 80, 81). The D_1 receptor has been shown to be critical for working memory function (82).

Revisions of the dopamine hypothesis for schizophrenia have posited diminished dopaminergic activity in the prefrontal cortex and a reciprocal dopaminergic hyperactivity in the mesolimbic pathways (83). Consistent with this model, chronic PCP administration also increases subcortical dopamine release, particularly in the nucleus accumbens (68, 84). Increased mesolimbic dopaminergic activity associated with long-term administration of PCP produces sensitization to the behavioral effects of NMDA receptor antagonists such as PCP, ketamine, and MK801 (85–87), dopamine agonists (88, 89), and stress (89). Chronic administration of PCP also leads to increased mesolimbic dopamine response to haloperidol (89). Together, these findings emphasize the reciprocal modulation of glutamate and dopamine neuronal systems and are consistent with the "sensitization model" of schizophrenia (90), which may account for the progressive course of the illness and the vulnerability to stress of individuals with the illness.

Antipsychotic Drugs and Glutamate

A characteristic feature of schizophrenia is the inability to adapt to an auditory stimulus that is preceded by a low-level warning tone, a response that is known as prepulse inhibition and is believed to reflect a defect in attentional

"filtering" of nonnovel stimuli (91). The atypical antipsychotic drugs clozapine, olanzapine, remoxipride, and quetiapine have all been found to reverse ketamine-induced deficits in prepulse inhibition (92–94). Haloperidol and selective antagonists at D_1, D_2 and serotonin$_2$ (5-HT_2) receptors did not correct the deficit in sensory gating caused by NMDA receptor antagonists (92, 95, 96), whereas the α_1-adrenergic antagonist prazosin blocked the disruptive effects of PCP (97). Chlorpromazine also blocks the effects of ketamine on prepulse inhibition, possibly by means of mediation by its potent antagonism of α_1-adrenergic receptors (96). Both clozapine and olanzapine attenuated the ketamine-induced increase in cortical metabolic activation measured by [^{14}C]-2-deoxyglucose in rats, an effect that was not achieved with either haloperidol or risperidone and that required a higher dose of olanzapine (10 mg/kg) than would be expected to produce maximal D_2 and 5-HT_2 blockade (98, 99). Corbett et al. (100) reported that olanzapine (0.25 mg/kg) and clozapine (2.5 mg/kg) but not haloperidol or risperidone reversed PCP-induced social withdrawal in rats. In another model, Olney (15) performed a series of experiments comparing the efficacy of antipsychotic drugs in preventing neuronal degeneration induced by NMDA receptor antagonists in the posterior cingulate and retrosplenial cortex in rats. Olanzapine, clozapine, and fluperlapine strongly prevented the neurotoxicity, whereas haloperidol and thioridazine displayed intermediate effectiveness (101–103). Neuroprotective effects have also been observed with muscarinic receptor antagonists, benzodiazepines, σ receptor ligands, and α_2-adrenergic receptor agonists, thereby making the clinical implications of activity in this complex model unclear (104).

Antipsychotic drugs can affect glutamatergic neurotransmission by modulating release of glutamate, by interacting with glutamate receptors, or by altering the density or subunit composition of glutamate receptors. Recent research has demonstrated that antipsychotic drugs acting through the D_2 receptor promote the phosphorylation of the NR_1 subunit of the NMDA receptor, thereby enhancing its function and consequent gene expression (105). Thus, dopamine-glutamate interactions occur intraneuronally as well as intrasynaptically (106). Free glutamate concentrations in the striatum measured by in vivo dialysis were increased by as much as fivefold by chronic administration of haloperidol or fluphenazine but were unaffected by clozapine (107–109). The augmentation of glutamate release in the striatum by conventional antipsychotic drugs appears to be mediated by D_2 inhibitory axoaxonic synapses on glutamatergic corticostriatal terminals (109), although long-term haloperidol treatment has also been shown to decrease expression of the glial glutamate transporter GLT-1 in the rat striatum (110). The elevation of excitatory amino acid concentrations may have important clinical consequences, as indicated by significant correlations between ratings of tardive dyskinesia and CSF concentrations of aspartate and glutamate in neuroleptic-treated patients (111, 112). In addition, perforated synapses in the caudate, which have been associated with haloperidol-induced extrapyramidal side effects, have been shown to occur in glutamatergic synapses and to be mediated by NMDA receptors (113).

Growing evidence suggests that the effects of certain atypical antipsychotics on NMDA receptors may differentiate these agents from conventional antipsychotics. Lidsky et al. (114) measured haloperidol and clozapine displacement of [^{3}H]MK801 binding in rat striatal and cortical membranes and found that haloperidol did not significantly interact with NMDA receptors at clinically relevant concentrations but that clozapine displaced the ligand from the NMDA receptor at therapeutic levels. Using intracellular recordings and a voltage clamp, Arvanov et al. (115) found that clozapine but not haloperidol produced an enhancement of NMDA-receptor-mediated neurotransmission. Both the selective 5-HT_{2A} antagonist M100907 and clozapine prevented PCP-induced blockade of NMDA receptors, as measured by depolarization of rat medial cortical pyramidal neurons (116), whereas selective D_2 blockers had no effect. Clozapine and several conventional agents have also been reported to act as partial agonists at the glycine modulatory site of the NMDA receptor, increasing neuronal depolarization at low concentrations and inhibiting depolarization at high concentrations (117, 118). Consistent with this interpretation, an increase in extracellular glycine attenuated the potentiation by haloperidol of NMDA-receptor-evoked response (119). In contrast, long-term administration of antipsychotics may result in desensitization of the glycine modulatory site of the NMDA receptor, as evidenced by a reduction in strychnine-insensitive glycine binding associated with both clozapine and conventional agents (120). These findings suggest that the glutamatergic effects of antipsychotics are importantly concentration-dependent and that, depending on their relative dose-response curves, different agents may act either as agonists or antagonists at therapeutic concentrations.

Several investigators have found that chronic antipsychotic treatment alters the expression of mRNA encoding glutamate receptor subunits, which varies depending on the drug type, the subunit, and the brain region (27, 121–123). In general, conventional antipsychotics increased the amount of mRNA encoding NMDA receptor subunits (NR_1 and NR_2) in the striatum, whereas clozapine treatment produced no change (122). This difference may reflect differential liability for extrapyramidal side effects. Conventional and atypical antipsychotics also differed in their effects on certain AMPA receptor subunits ($GluR_2$ and $GluR_4$), whereas $GluR_1$ was increased and $GluR_3$ decreased by both haloperidol and clozapine (123). Dissimilarities also were found for kainic acid receptors, with only clozapine reported to elevate expression of mRNA encoding $GluR_6$, $GluR_7$, and KA2 (123).

Pharmacologic Interventions at Glutamate Receptors

Evidence for hypoactivity of NMDA receptors in schizophrenia has led to therapeutic trials with agents that indirectly activate the receptor. Direct agonists at the NMDA receptor have not been studied because of the risk that excessive stimulation may cause excitotoxic damage to neurons (124). A more promising target is the glycine modulatory site on the NMDA receptor. Early trials of glycine administered orally at doses of 5–15 g/day produced inconsistent results, probably because glycine poorly crosses the blood-brain barrier (125–128). More recently, Javitt, Heresco-Levy, and colleagues (129–131) performed a series of placebo-controlled crossover trials with high doses of glycine (30–60 g/day) added to antipsychotic drugs and have demonstrated selective improvement in negative symptoms. In a 6-week trial, glycine also significantly improved subjects' ratings on the cognitive subscale of the Positive and Negative Syndrome Scale (131). Javitt and colleagues (23) demonstrated that glycine inhibits PCP-induced stimulation of subcortical dopamine release in a dose-related fashion in rats. Glycine transport inhibitors were also found to block PCP-induced behavioral hyperactivity (23), and they may represent a potential therapeutic approach. In another therapeutic approach with a full agonist at the glycine modulatory site, Tsai et al. (132) added D-serine to ongoing antipsychotic medication at a daily dose of 30 mg/kg for 8 weeks and reported significant improvements, compared to effects of placebo, in negative symptoms, psychosis, and cognitive function as measured by the cognitive subscale of the Positive and Negative Syndrome Scale and performance on the Wisconsin Card Sorting Test.

In a related approach, several groups have administered D-cycloserine, an antitubercular drug that acts as a relatively selective partial agonist at the glycine modulatory site over a narrow range of concentrations (133). Compared to glycine, D-cycloserine produces approximately 60% activation of the NMDA receptor, thus acting as an agonist in the presence of low concentrations of glycine (and related endogenous agonists) and as an antagonist in the presence of high concentrations of glycine. In an initial placebo-controlled, partly blinded, dose-finding study of D-cycloserine added to conventional neuroleptics, Goff et al. (134) found an inverted U-shaped dose response with significant reductions in negative symptoms and improvement in performance on a test of working memory at a D-cycloserine dose of 50 mg/day. Van Berkel et al. (135) administered D-cycloserine in a small, open trial to medication-free schizophrenia patients and observed selective improvement of negative symptoms at a D-cycloserine dose of 100 mg/day. In an 8-week, fixed-dose, placebo-controlled, parallel-group trial involving 46 patients who met criteria for the deficit syndrome of schizophrenia (126), 50 mg/day of D-cycloserine significantly improved negative symptoms when added to conventional antipsychotics, but it did not improve performance on a cognitive battery (136). It is noteworthy that a full response was not achieved until weeks 4–6. Rosse et al. (137) found no improvement in negative symptoms when 15 mg/day or 30 mg/day of D-cycloserine was added to molindone.

Since clozapine (arguably) produces substantial therapeutic effects on negative symptoms in patients who respond poorly to typical neuroleptics and since its effects on glutamatergic systems differ from those of conventional agents, it was of interest to determine whether the addition of D-cycloserine would have further ameliorative effects in clozapine responders. Two separate trials of 50 mg/day of D-cycloserine added to clozapine resulted in worsening of negative symptoms (138, 139). In contrast, controlled trials in which the full agonists glycine and D-serine were added to clozapine produced no change in negative symptoms or cognitive function (140–142). One possible explanation for these findings is that clozapine may exert its effects on negative symptoms partly by increasing occupancy of the glycine modulatory site on the NMDA receptor, thereby transforming the partial agonist D-cycloserine into an antagonist and precluding additional therapeutic effects with the exogenous full agonists glycine and D-serine.

A final but quite preliminary area of investigation involves the study of drugs acting at the AMPA receptor that have recently become available for clinical trials. This family of drugs, known as ampakines, act as positive modulators of the AMPA receptor complex. CX516, the first drug of this class to be studied, has been shown to increase the peak and duration of glutamate-induced AMPA receptor-gated inward currents (143). In rats, ampakines increased hippocampal neuronal activity in response to stimulation of glutamatergic afferents and enhanced long-term potentiation (144, 145). These findings suggest that ampakines, by potentiating AMPA receptor-induced depolarization, indirectly enhance NMDA receptor function. In behavioral models to test learning in rats, ampakines improved acquisition and retention in the radial arm maze, water maze, and olfactory cue tasks (146). CX516 also synergistically blocked methamphetamine-induced rearing behavior in rats when it was added to clozapine and to conventional antipsychotic agents, an effect believed to predict antipsychotic efficacy (147).

CX516 was added to clozapine in a placebo-controlled, 4-week, escalating-dose trial involving six patients with schizophrenia and in a placebo-controlled, fixed-dose, parallel-group design with an additional 13 patients; the combination was well tolerated without significant adverse effects (148). Combined results from the two trials (N=19) revealed a consistent pattern of improvement in performance on tests of attention, memory, and distractibility. Comparisons between groups demonstrated moderate-to-large effect sizes favoring CX516 over placebo for most cognitive tests, but inferential tests of statistical sig-

nificance were not performed due to the small number of subjects. Although the ampakines show promise as a treatment for cognitive deficits of schizophrenia, these preliminary data require replication in larger groups of patients.

Conclusions

Multiple lines of evidence have linked abnormalities in glutamatergic receptor expression, subunit composition, and function in schizophrenia. Similarities between behavioral effects of NMDA receptor antagonists and the clinical symptoms of schizophrenia have focused attention on treatment trials targeting a putative hypoactivity of a subpopulation of NMDA receptors. However, currently available antipsychotic drugs alter glutamatergic activity in multiple ways by enhancing release of glutamate in the striatum, directly interacting with NMDA receptors, altering glutamate receptor density, and changing the subunit composition of glutamate receptors. Many of these effects are regionally selective and vary among the antipsychotic drugs, with important differences emerging between atypical and conventional drugs. Clinical trials in which NMDA receptor activity was enhanced by agents acting at the glycine modulatory site have demonstrated decreases in negative symptoms and variable improvements in cognitive function. Electrophysiologic and neurochemical evidence suggests that clozapine, aside from its interactions with aminergic receptors, may also be acting through the NMDA receptor in affecting negative symptoms. Although the findings are preliminary, recent work with an ampakine indicates that positive modulation of the AMPA receptor may also provide another glutamatergic approach to treat cognitive deficits in schizophrenia. Thus, drugs that modulate glutamatergic neurotransmission hold promise for novel treatments for schizophrenia, especially for the cognitive impairments and negative symptoms associated with the disorder.

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Supported in part by NIMH grants MH-51290 and MH-606450 (to Dr. Coyle) and MH-54245 and MH-57708 (to Dr. Goff).

References

1. Krystal JH, D'Souza DC, Petrakis IL, Belger A, Berman R, Charney DS, Abi-Saab W, Madonick S: NMDA agonists and antagonists as probes of glutamatergic dysfunction and pharmacotherapies for neuropsychiatric disorders. Harv Rev Psychiatry 1999; 7:125–133
2. Goff DC: Glutamate receptors in schizophrenia and antipsychotic drugs, in Neurotransmitter Receptors in Actions of Antipsychotic Medications. Edited by Lidow MS. New York, CRC Press, 2000, pp 121–136
3. Meador-Woodruff JH, Healy DJ: Glutamate receptor expression in schizophrenic brain. Brain Res Rev 2000; 31:288–294
4. Gao X-M, Sakai K, Roberts RC, Conley RR, Dean B, Tamminga CA: Ionotropic glutamate receptors and expression of *N*-methyl-D-aspartate receptor subunits in subregions of human hippocampus: effects of schizophrenia. Am J Psychiatry 2000; 157:1141–1149
5. Ibrahim HM, Hogg AJ Jr, Healy DJ, Haroutunian V, Davis KL, Meador-Woodruff JH: Ionotropic glutamate receptor binding and subunit mRNA expression in thalamic nuclei in schizophrenia. Am J Psychiatry 2000; 157:1811–1823
6. Heckers S, Goff D, Schacter D, Savage C, Fischman A, Alpert N, Rausch S: Functional imaging of memory retrieval in deficit vs nondeficit schizophrenia. Arch Gen Psychiatry 1999; 56:1117–1123
7. Heckers S, Curran T, Goff D, Rauch SL, Fischman AJ, Alpert NM, Schacter DL: Abnormalities in the thalamus and prefrontal cortex during episodic object recognition in schizophrenia. Biol Psychiatry 2000; 48:651–657
8. Akbarian S, Bunney WJ, Potkin S, Wigal S, Hagman J, Sandman C, Jones E: Altered distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase cells in frontal lobe of schizophrenics implies disturbances of cortical development. Arch Gen Psychiatry 1993; 50:169–177
9. Akbarian S, Vinuela A, Kim J, Potkin S, Bunney WJ, Jones E: Distorted distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase neurons in temporal lobe of schizophrenics implies anomalous cortical development. Arch Gen Psychiatry 1993; 50:178–187
10. McGlashan TH, Hoffman RE: Schizophrenia as a disorder of developmentally reduced synaptic connectivity. Arch Gen Psychiatry 2000; 57:637–648
11. McDonald JW, Johnston MV: Physiological and pathophysiological roles of excitatory amino acids during central nervous system development. Brain Res Rev 1990; 15:41–70
12. Kerwin RW: Glutamate receptor, microtubule associated proteins and developmental anomaly in schizophrenia: an hypothesis. Psychol Med 1993; 13:547–551
13. Komuro H, Rakic P: Modulation of neuronal migration by NMDA receptors. Science 1993; 260:95–97
14. Choi DW: Glutamate neurotoxicity and diseases of the nervous system. Neuron 1988; 1:623–634
15. Olney JW: New mechanisms of excitatory transmitter neurotoxicity. J Neural Transm Suppl 1994; 43:47–51
16. Carlsson M, Carlsson A: Interactions between glutamatergic and monoaminergic systems within the basal ganglia—implications for schizophrenia and Parkinson's disease. Trends Neurosci 1990; 13:272–276
17. Nakanishi S: Molecular diversity of glutamate receptors and implications for brain function. Science 1992; 258:597–603
18. Dawson TM, Zhang J, Dawson VL, Snyder SH: Nitric oxide: cellular regulation and neuronal injury. Prog Brain Res 1994; 103:365–369
19. Jentsch J, Roth R: The neuropsychopharmacology of phencyclidine: from NMDA receptor hypofunction to the dopamine hypothesis of schizophrenia. Neuropsychopharmacology 1999; 20:201–225
20. Huettner JE: Competitive antagonism of glycine at the *N*-methyl-D-aspartate (NMDA) receptor. Biochem Pharmacol 1991; 41:9–16
21. Bergeron R, Meyer T, Coyle J, Greene R: Modulation of *N*-methyl-D-aspartate receptor function by glycine transport. Proc Natl Acad Sci USA 1998; 95:15730–15734
22. Danysza W, Parsons CG: Glycine and *N*-methyl-D-aspartate receptors: physiological significance and possible therapeutic applications. J Neurophysiol 1998; 80:3336–3340

23. Javitt DC, Balla A, Sershen H, Lajtha A: Reversal of the behavioral and neurochemical effects of phencyclidine by glycine and glycine transport inhibitors. Biol Psychiatry 1999; 45:668–679
24. Bliss T, Collingridge G: A synaptic model of memory: long-term potentiation in the hippocampus. Nature 1993; 361:31–39
25. Kuner T, Schoepfer R: Multiple structural elements determine subunit specificity of Mg^{2+} block in NMDA receptor channels. J Neurosci 1996; 16:3549–3558
26. Grunze HC, Rainnie DG, Hasselmo ME, Barkai E, Hearn EF, McCarley RW, Greene RW: NMDA-dependent modulation of CA1 local circuit inhibition. J Neurosci 1996; 16:2034–2043
27. Fitzgerald LW, Deutch AY, Gasic G, Heinemann SF, Nestler EJ: Regulation of cortical and subcortical glutamate receptor subunit expression by antipsychotic drugs. J Neurosci 1995; 15: 2453–2461
28. Breese CR, Freedman R, Leonard SS: Glutamate receptor subtype expression in human postmortem brain tissue from schizophrenics and alcohol abusers. Brain Res 1995; 674:82–90
29. Kim JS, Kornhuber HH, Schmid-Burgk W, Holzmuller B: Low cerebrospinal glutamate in schizophrenic patients and a new hypothesis on schizophrenia. Neurosci Lett 1980; 20:379–382
30. Bjerkenstedt L, Edman G, Hagenfeldt L, Sedvall G, Wiesel FA: Plasma amino acids in relation to cerebrospinal fluid monoamine metabolites in schizophrenic patients and healthy controls. Br J Psychiatry 1985; 147:276–282
31. Macciardi F, Lucca A, Catalano M, Marino C, Zanardi R, Smeraldi E: Amino acid patterns in schizophrenia: some new findings. Psychiatry Res 1989; 32:63–70
32. Gattaz WF, Gattaz D, Beckmann H: Glutamate in schizophrenics and healthy controls. Arch Psychiatr Nervenkr 1982; 231:221–225
33. Perry TL: Normal cerebrospinal fluid and brain glutamate levels in schizophrenia do not support the hypothesis of glutamatergic neuronal dysfunction. Neurosci Lett 1982; 28:81–85
34. Tsai G, van Kammen D, Chen S, Kelley M, Grier A, Coyle J: Glutamatergic neurotransmission involves structural and clinical deficits of schizophrenia. Biol Psychiatry 1998; 44:667–674
35. Tsai G, Passani LA, Slusher BS, Carter R, Baer L, Kleinman JE, Coyle JT: Abnormal excitatory neurotransmitter metabolism in schizophrenic brains. Arch Gen Psychiatry 1995; 52:829–836
36. Coyle J: The nagging question of the function of *N*-acetylaspartylglutamate. Neurobiol Dis 1997; 4:231–238
37. Kegles L, Humaran TJ, Mann JJ: In vivo neurochemistry of brain in schizophrenia as revealed by magnetic resonance spectroscopy. Biol Psychiatry 1998; 44:382–388
38. Tsai G, Coyle JT: *N*-Acetylaspartate in neuropsychiatric disorders. Prog Neurobiol 1995; 46:531–540
39. Deakin JFW, Slater P, Simpson MDC, Gilchrist AC, Skan WJ, Royston MC, Reynolds GP, Cross AJ: Frontal cortical and left temporal glutamatergic dysfunction in schizophrenia. J Neurochem 1989; 52:1781–1786
40. Nishikawa T, Takashima M, Toru M: Increased [^{3}H] kainic acid binding in the prefrontal cortex in schizophrenia. Neurosci Lett 1983; 40:245–250
41. Kerwin RW, Patel S, Meldrum BS, Czudek C, Reynolds GP: Asymmetrical loss of glutamate receptor subtype in left hippocampus in schizophrenia. Lancet 1988; 1:583–584
42. Kerwin R, Patel S, Meldrum B: Quantitative autoradiographic analysis of glutamate binding sites in the hippocampal formation in normal and schizophrenic brain post mortem. Neuroscience 1990; 39:25–32
43. Ishimaru M, Kurumaji A, Toru M: NMDA-associated glycine binding site increases in schizophrenic brains (letter). Biol Psychiatry 1992; 32:379–381
44. Ishimaru M, Kurumaji A, Toro M: Increases in strychnine-insensitive glycine binding sites in cerebral cortex of chronic schizophrenics: evidence for glutamate hypothesis. Biol Psychiatry 1994; 35:84–95
45. Simpson MDC, Slater P, Royston MC, Deaking JFW: Regionally selective deficits in uptake sites for glutamate and gamma-aminobutyric acid in the basal ganglia in schizophrenia. Psychiatry Res 1992; 42:273–282
46. Harrison PJ, McLaughlin D, Kerwin RW: Decreased hippocampal expression of a glutamate receptor gene in schizophrenia. Lancet 1991; 337:450–452
47. Eastwood SL, McDonald B, Burnet PWJ, Beckwith JP, Kerwin RW, Harrison PJ: Decreased expression of mRNAs encoding non-NMDA glutamate receptors GluR1 and GluR2 in medial temporal lobe neurons in schizophrenia. Mol Brain Res 1995; 29: 211–223
48. Akbarian S, Sucher NJ, Bradley D, Tafazzoli A, Trinh D, Hetrick WP, Potkin SG, Sandman CA, Bunney WE, Jones EG: Selective alterations in gene expression for NMDA receptor subunits in prefrontal cortex of schizophrenics. J Neurosci 1996; 16:19–30
49. Mohn A, Gainetdinov P, Caron M, Koller B: Mice with reduced NMDA receptor expression display behaviors related to schizophrenia. Cell 1999; 98:427–436
50. Luby ED, Cohen BD, Rosenbaum G, Gottlieb JS, Kelley R: Study of a new schizophrenomimetic drug—sernyl. Arch Neurol Psychiatry 1959; 81:363–369
51. Javitt DC, Zukin SR: Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 1991; 148:1301–1308
52. Itil T, Keskiner A, Kiremitci N, Holden JMC: Effect of phencyclidine in chronic schizophrenics. Can Psychiatr Assoc J 1967; 12: 209–212
53. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MBJ, Charney DS: Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans: psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 1994; 51:199–214
54. Cohen B, Rosenbaum G, Luby E, Gottlieb J: Comparison of phencyclidine hydrochloride (sernyl) with other drugs: simulation of schizophrenic performance with phencyclidine hydrochloride (sernyl), lysergic acid diethylamide (LSD-25), and amobarbital (Amytal) sodium, II: symbolic and sequential thinking. Arch Gen Psychiatry 1962; 6:79–85
55. Moller P, Husby R: The initial prodrome in schizophrenia: searching for core dimensions of experience and behavior. Schizophr Bull 2000; 26:217–232
56. Malhotra A, Pinals D, Weingartner H, Sirocco K, Missar C, Pickar D, Breier A: NMDA receptor function and human cognition: the effects of ketamine in healthy volunteers. Neuropsychopharmacology 1996; 14:301–307
57. Newcomer J, Farber N, Jevtovic-Todorovic V, Selke G, Melson A, Hershey T, Craft S, Olney J: Ketamine-induced NMDA receptor hypofunction as a model of memory impairment and psychosis. Neuropsychopharmacology 1999; 20:106–118
58. Lahti AC, Koffel B, LaPorte D, Tamminga CA: Subanesthetic doses of ketamine stimulate psychosis in schizophrenia. Neuropsychopharmacology 1995; 13:9–19
59. Malhotra A, Pinals D, Adler C, Elman I, Clifton A, Pickar D, Breier A: Ketamine-induced exacerbation of psychotic symptoms and cognitive impairment in neuroleptic-free schizophrenics. Neuropsychopharmacology 1997; 17:141–150
60. Krystal JH, Belger A, D'Souza C, Anand A, Charney DS, Aghajanian GK, Moghaddam B: Therapeutic implications of the hyperglutamatergic effects of NMDA antagonists. Neuropsychopharmacology 1999; 22:S143–S157
61. Breier A, Malhotra A, Pinals DA, Weisenfeld NI, Pickar D: Association of ketamine-induced psychosis with focal activation of

the prefrontal cortex in healthy volunteers. Am J Psychiatry 1997; 154:805–811
62. Lahti AC, Holcomb HH, Medoff DR, Tamminga CA: Ketamine activates psychosis and alters limbic blood flow in schizophrenia. Neuroreport 1995; 6:869–872
63. Vollenweider FX, Leenders KL, Oye I, Hell D, Angst J: Differential psychopathology and patterns of cerebral glucose utilisation produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). Eur Neuropsychopharmacol 1997; 7:25–38
64. Vollenweider FX, Leenders KL, Scharfetter C, Antonini A, Maguire P, Missimer J, Angst J: Metabolic hyperfrontality and psychopathology in the ketamine model of psychosis using positron emission tomography (PET) and [^{18}F] fluorodeoxyglucose (FDG). Eur Neuropsychopharmacol 1997; 7:9–24
65. Hertzmann M, Reba RC, Kotlyarove EV: Single photon emission computed tomography in phencyclidine and related drug abuse (letter). Am J Psychiatry 1990; 147:255–256
66. Wu JC, Buchsbaum MS, Bunney EW: Positron emission tomography study of phencyclidine users as a possible drug model of schizophrenia. Yakubutsu Seishin 1991; 11:47–48
67. Jentsch J, Redmond DJ, Elsworth J, Taylor J, Youngren K, Roth R: Enduring cognitive deficits and cortical dopamine dysfunction in monkeys after long-term administration of phencyclidine. Science 1997; 277:953–955
68. Deutch AY, Tam S-Y, Freeman AS, Bowers MBJ, Roth RH: Mesolimbic and mesocortical dopamine activation induced by phencyclidine: contrasting pattern to striatal response. Eur J Pharmacol 1987; 134:257–264
69. Bowers MBJ, Bannon MJ, Hoffman FJJ: Activation of forebrain dopamine systems by phencyclidine and footshock stress: evidence for distinct mechanisms. Psychopharmacology (Berl) 1987; 93:133–135
70. Verma A, Moghaddam B: NMDA receptor antagonists impair prefrontal cortex function as assessed via spatial delayed alternation performance in rats: modulation by dopamine. J Neurosci 1996; 16:373–379
71. Moghaddam B, Adams B, Verma A, Daly D: Activation of glutamatergic neurotransmission by ketamine: a novel step in the pathway from NMDA receptor blockade to dopaminergic and cognitive disruptions associated with the prefrontal cortex. J Neurosci 1997; 17:2921–2927
72. Svensson TH, Mathe JM, Andersson JL, Nomikos GG, Hildebrand BE, Marcus M: Mode of action of atypical neuroleptics in relation to the phencyclidine model of schizophrenia: role of 5-HT_2 receptor and alpha$_1$-adrenoreceptor antagonism. J Clin Psychopharmacol 1995; 15:11S–18S
73. Smith GS, Schloesser R, Brodie JD, Dewey SL, Logan J, Vitkun SA, Simkowitz P, Hurley A, Cooper T, Volkow ND, Cancro R: Glutamate modulation of dopamine measured in vivo with positron emission tomography (PET) and ^{11}C-raclopride in normal human subjects. Neuropsychopharmacology 1998; 18:18–25
74. Breier A, Adler CM, Weisenfeld N, Su TP, Elman I, Picken L, Malhotra AK, Pickar D: Effects of NMDA antagonism on striatal dopamine release in healthy subjects: application of a novel PET approach. Synapse 1998; 29:142–147
75. Vollenweider FX, Vontobel P, Oye I, Hell D, Leenders KL: Effects of (S)-ketamine on striatal dopamine: a [^{11}C]raclopride PET study of a model psychosis in humans. J Psychiatr Res 2000; 34:35–43
76. Tsukada H, Harada N, Nishiyama S, Ohba H, Sato K, Fukumoto D, Kakiuchi T: Ketamine decreased striatal [^{11}C]raclopride binding with no alterations in static dopamine concentrations in the striatal extracellular fluid in the monkey brain: multiparametric PET studies combined with microdialysis analysis. Synapse 2000; 37:95–103
77. Jentsch J, Tran A, Le D, Youngren K, Roth R: Subchronic phencyclidine administration reduces mesoprefrontal dopamine utilization and impairs prefrontal cortical-dependent cognition in the rat. Neuropsychopharmacology 1997; 17:92–99
78. Jentsch JD, Dazzi L, Chhatwal JP, Verrico CD, Roth RH: Reduced prefrontal dopamine, but not acetylcholine, release in vivo after repeated, intermittent phencyclidine administration to rats. Neurosci Lett 1998; 24:175–178
79. Lindefors N, Barati S, O'Connor W: Differential effects of single and repeated ketamine administration on dopamine, serotonin, and GABA transmission in rat prefrontal cortex. Brain Res 1997; 759:202–212
80. Healy DJ, Meador-Woodruff JH: Differential regulation, by MK-801, of dopamine receptor gene expression in rat nigrostriatal and mesocorticolimbic systems. Brain Res 1996; 708:38–44
81. Healy DJ, Meador-Woodruff JH: Dopamine receptor gene expression in hippocampus is differentially regulated by the NMDA receptor antagonist MK-801. Eur J Pharmacol 1996; 306:257–264
82. Sawaguchi T, Goldman-Rakic PS: D_1 dopamine receptors in prefrontal cortex: involvement in working memory. Science 1991; 251:947–950
83. Davis KL, Kahn RS, Ko G, Davidson M: Dopamine in schizophrenia: a review and reconceptualization. Am J Psychiatry 1991; 148:1474–1486
84. Jentsch J, Elsworth J, Redmond DJ, Roth R: Phencyclidine increases forebrain monoamine metabolism in rats and monkeys: modulation by the isomers of HA966. J Neurosci 1997; 17:1769–1776
85. Scalzo F, Holson R: The ontogeny of behavioral sensitization to phencyclidine. Neurotoxicol Teratol 1992; 14:7–14
86. Wolf M, Diener J, Lajeunesse C, Shriqui C: Low-dose bromocriptine in neuroleptic-resistant schizophrenia: a pilot study. Biol Psychiatry 1992; 31:1166–1168
87. Xu X, Domino E: Phencyclidine-induced behavioral sensitization. Pharmacol Biochem Behav 1994; 47:603–608
88. Lannes B, Micheletti G, Warter J, Kempf E, DiScala G: Behavioral, pharmacological, and biochemical effects of acute and chronic administration of ketamine in the rat. Neurosci Lett 1991; 128:177–181
89. Jentsch J, Taylor J, Roth R: Subchronic phencyclidine administration increases mesolimbic dopamine system responsivity and augments stress and amphetamine-induced hyperlocomotion. Neuropsychopharmacology 1998; 19:105–113
90. Lieberman J, Sheitman B, Kinon B: Neurochemical sensitization in the pathophysiology of schizophrenia: deficits and dysfunction in neuronal regulation and plasticity. Neuropsychopharmacology 1997; 17:205–229
91. Braff DL, Geyer MA: Sensorimotor gating and schizophrenia. Arch Gen Psychiatry 1990; 47:181–188
92. Bakshi VP, Swerdlow NR, Geyer MA: Clozapine antagonizes phencyclidine-induced deficits in sensorimotor gating of the startle response. J Pharmacol Exp Ther 1994; 271:787–794
93. Bakshi V, Geyer M: Antagonism of phencyclidine-induced deficits in prepulse inhibition by the putative atypical antipsychotic drug olanzapine. Psychopharmacology (Berl) 1995; 122: 198–201
94. Swerdlow N, Bakshi V, Geyer M: Seroquel restores sensorimotor gating in phencyclidine-treated rats. J Pharmacol Exp Ther 1996; 279:1290–1299
95. Johansson C, Jackson D, Svensson L: The atypical antipsychotic, remoxipride, blocks phencyclidine-induced disruption of prepulse inhibition in the rat. Psychopharmacology (Berl) 1994; 116:437–442
96. Swerdlow N, Bakshi V, Waikar M, Taaid N, Geyer M: Seroquel, clozapine and chlorpromazine restore sensorimotor gating in

ketamine-treated rats. Psychopharmacology (Berl) 1998; 140: 75–80
97. Bakshi VP, Geyer MA: Reversal of phencyclidine-induced deficits in prepulse inhibition by prazosin, an alpha-1 adrenergic antagonist. J Pharmacol Exp Ther 1997; 283:666–674
98. Duncan GE, Leipzig JN, Mailman RB, Lieberman JA: Differential effects of clozapine and haloperidol on ketamine-induced brain metabolic activation. Brain Res 1998; 812:65–75
99. Duncan GE, Miyamoto S, Leipzig JN, Lieberman JA: Comparison of the effects of clozapine, risperidone, and olanzapine on ketamine-induced alterations in regional brain metabolism. J Pharmacol Exp Ther 2000; 293:8–14
100. Corbett R, Camacho F, Woods AT, Kerman LL, Fishkin RJ, Brooks K, Dunn RW: Antipsychotic agents antagonize non-competitive *N*-methyl-D-aspartate antagonist-induced behaviors. Psychopharmacology (Berl) 1995; 120:67–74
101. Olney JW, Farber NB: Efficacy of clozapine compared with other antipsychotics in preventing NMDA-antagonist neurotoxicity. J Clin Psychiatry 1994; 55(9, suppl B):43–46
102. Farber N, Foster J, Duhan N, Olney J: Olanzapine and fluperlapine mimic clozapine in preventing MK-801 neurotoxicity. Schizophr Res 1996; 21:33–37
103. Farber NB, Price MT, Labruyere J, Nemnich J, St Peter H, Wozniak DF, Olney JW: Antipsychotic drugs block phencyclidine receptor-mediated neurotoxicity. Biol Psychiatry 1993; 34: 119–121
104. Olney JW, Farber NB: Glutamate receptor dysfunction and schizophrenia. Arch Gen Psychiatry 1995; 52:998–1007
105. Leveque JC, Macias W, Rajadhyaksha A, Carlson RR, Barczak A, Kang S, Li X-M, Coyle JT, Huganier RL, Heckers S, Konradi C: Intracellular modulation of NMDA receptor function by antipsychotic drugs. J Neurosci 2000; 20:4011–4020
106. Snyder GI, Allen PB, Feinberg AA, Valle CG, Huganier RI, Nairn AC, Greengard P: Regulation of phosphorylation of the GluR1 AMPA receptor in the neostriatum by dopamine and stimulants in vivo. J Neurosci 2000; 20:4480–4488
107. Yamamoto BK, Cooperman MA: Differential effects of chronic antipsychotic drug treatment on extracellular glutamate and dopamine concentrations. J Neurosci 1994; 14:4159–4166
108. Yamamoto BK, Pehek EA, Meltzer HY: Brain region effects of clozapine on amino acid and monoamine transmission. J Clin Psychiatry 1994; 55(9, suppl B):8–14
109. See R, Lynch A: Duration-dependent increase in striatal glutamate following prolonged fluphenazine administration in rats. Eur J Pharmacol 1996; 308:279–282
110. Schneider J, Wade T, Lidsky T: Chronic neuroleptic treatment alters expression of glial glutamate transporter GLT-1 mRNA in the striatum. Neuroreport 1998; 9:133–136
111. Goff DC, Tsai G, Beal MF, Coyle JT: Tardive dyskinesia and substrates of energy metabolism in CSF. Am J Psychiatry 1995; 152: 1730–1736
112. Tsai G, Goff DC, Chang RW, Flood J, Baer L, Coyle JT: Markers of glutamatergic neurotransmission and oxidative stress associated with tardive dyskinesia. Am J Psychiatry 1998; 155:1207–1213
113. Meshul C, Bunker G, Mason J, Allen C, Janowsky A: Effects of subchronic clozapine and haloperidol on striatal glutamatergic synapses. J Neurochem 1996; 67:1965–1973
114. Lidsky TI, Yablonsky-Alter E, Zuck L, Banerjee SP: Antiglutamatergic effects of clozapine. Neurosci Lett 1993; 163: 155–158
115. Arvanov V, Liang X, Schwartz J, Grossman S, Wang R: Clozapine and haloperidol modulate *N*-methyl-D-aspartate and non-*N*-methyl-D-aspartate receptor-mediated neurotransmission in rat prefrontal cortical neurons in vitro. J Pharmacol Exp Ther 1997; 283:226–234
116. Wang RY, Liang X: M100907 and clozapine, but not haloperidol or raclopride, prevent phencyclidine-induced blockade of NMDA responses in pyramidal neurons of the rat medial prefrontal cortical slice. Neuropsychopharmacology 1998; 19:74–85
117. Banerjee SP, Zuck LG, Yablonsky-Alter E, Lidsky TI: Glutamate agonist activity: implications for antipsychotic drug action and schizophrenia. Neuroreport 1995; 6:2500–2504
118. Lidsky TI, Yablonsky-Alter E, Zuck LG, Banerjee SP: Antipsychotic drug effects on glutamatergic activity. Brain Res 1997; 764:46–52
119. Fletcher EJ, MacDonald JF: Haloperidol interacts with the strychnine-insensitive glycine site at the NMDA receptor in cultured mouse hippocampal neurones. Eur J Pharmacol 1993; 235:291–295
120. McCoy L, Richfield EK: Chronic antipsychotic treatment alters glycine-stimulated NMDA receptor binding in rat brain. Neurosci Lett 1996; 213:137–141
121. Healy D, Meador-Woodruff J: Clozapine and haloperidol differentially affect AMPA and kainate receptor subunit mRNA levels in rat cortex and striatum. Mol Brain Res 1997; 47:331–338
122. Riva M, Tascedda F, Lovati E, Racagni G: Regulation of NMDA receptor subunit messenger RNA levels in the rat brain following acute and chronic exposure to antipsychotic drugs. Mol Brain Res 1997; 50:136–142
123. Meador-Woodruff J, King R, Damask S, Bovenkerk K: Differential regulation of hippocampal AMPA and kainate receptor subunit expression by haloperidol and clozapine. Mol Psychiatry 1996; 1:41–53
124. Lawlor BA, Davis KL: Does modulation of glutamatergic function represent a viable therapeutic strategy in Alzheimer's disease? Biol Psychiatry 1992; 31:337–350
125. Waziri R: Glycine therapy of schizophrenia (letter). Biol Psychiatry 1988; 23:209–214
126. Rosse RB, Theut SK, Banay-Schwartz M, Leighton M, Scarcella E, Cohen CG, Deutsch SI: Glycine adjuvant therapy to conventional neuroleptic treatment in schizophrenia: an open-label, pilot study. Clin Neuropharmacol 1989; 12:416–424
127. Costa J, Khaled E, Sramek J, Bunney W, Potkin SG: An open trial of glycine as an adjunct to neuroleptics in chronic treatment-refractory schizophrenics (letter). J Clin Psychopharmacol 1990; 10:71–72
128. D'Souza DC, Charney D, Krystal J: Glycine site agonists of the NMDA receptor: a review. CNS Drug Rev 1995; 1:227–260
129. Javitt DC, Zylberman I, Zukin SR, Heresco-Levy U, Lindenmayer JP: Amelioration of negative symptoms in schizophrenia by glycine. Am J Psychiatry 1994; 151:1234–1236
130. Heresco-Levy U, Javitt D, Ermilov M, Mordel C, Horowitz A, Kelly D: Double-blind, placebo-controlled, crossover trial of glycine adjuvant therapy for treatment-resistant schizophrenia. Br J Psychiatry 1996; 169:610–617
131. Heresco-Levy U, Javitt D, Ermilov M, Mordel C, Silipo G, Lichenstein M: Efficacy of high-dose glycine in the treatment of enduring negative symptoms of schizophrenia. Arch Gen Psychiatry 1999; 56:29–36
132. Tsai G, Yang P, Chung L-C, Lange N, Coyle J: D-Serine added to antipsychotics for the treatment of schizophrenia. Biol Psychiatry 1998; 44:1081–1089
133. Watson GB, Bolanowski MA, Baganoff MP, Deppeler CL, Lanthorn TH: D-Cycloserine acts as a partial agonist at the glycine modulatory site of the NMDA receptor expressed in Xenopus oocytes. Brain Res 1990; 510:158–160
134. Goff DC, Tsai G, Manoach DS, Coyle JT: Dose-finding trial of D-cycloserine added to neuroleptics for negative symptoms in schizophrenia. Am J Psychiatry 1995; 152:1213–1215
135. van Berckel BN, Hijman R, van der Linden JA, Westenberg HG, van Ree JM, Kahn RS: Efficacy and tolerance of D-cycloserine in

drug-free schizophrenic patients. Biol Psychiatry 1996; 40: 1298–1300

136. Goff D, Tsai G, Levitt J, Amico E, Manoach D, Schoenfeld D, Hayden D, McCarley R, Coyle J: A placebo-controlled trial of D-cycloserine added to conventional neuroleptics in patients with schizophrenia. Arch Gen Psychiatry 1999; 56:21–27
137. Rosse R, Fay-McCarthy M, Kendrick K, Davis R, Deutsch S: D-Cycloserine adjuvant therapy to molindone in the treatment of schizophrenia. Clin Neuropharmacol 1996; 19:444–450
138. Goff DC, Tsai G, Manoach DS, Flood J, Darby DG, Coyle JT: D-Cycloserine added to clozapine for patients with schizophrenia. Am J Psychiatry 1996; 153:1628–1630
139. Goff D, Henderson D, Evins A, Amico E: A placebo-controlled crossover trial of D-cycloserine added to clozapine in patients with schizophrenia. Biol Psychiatry 1999; 45:512–514
140. Potkin SG, Jin Y, Bunney BG, Costa J, Gulasekaram B: Effect of clozapine and adjunctive high-dose glycine in treatment-resistant schizophrenia. Am J Psychiatry 1999; 156:145–147
141. Tsai GE, Yang P, Chung L-C, Tsai I-C, Tsai C-W, Coyle JT: D-Serine added to clozapine for the treatment of schizophrenia. Am J Psychiatry 1999; 156:1822–1825
142. Evins AE, Fitzgerald SM, Wine L, Roselli R, Goff DC: Placebo-controlled trial of glycine added to clozapine in schizophrenia. Am J Psychiatry 2000; 157:826–828
143. Arai A, Kessler M, Rogers G, Lynch G: Effects of a memory-enhancing drug on DL-alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor currents and synaptic transmission in hippocampus. J Pharmacol Exp Ther 1996; 278:1–12
144. Staubli U, Perez Y, Xu F, Rogers G, Ingvar M, Stone-Elander S, Lynch G: Centrally active modulators of glutamate receptors facilitate the induction of long-term potentiation in vivo. Proc Natl Acad Sci USA 1994; 91:11158–11162
145. Sirvio J, Larson J, Quach L, Rogers G, Lynch G: Effects of pharmacologically facilitating glutamatergic transmission in the trisynaptic intrahippocampal circuit. Neuroscience 1996; 74: 1025–1035
146. Staubli U, Rogers G, Lynch G: Facilitation of glutamate receptors enhances memory. Proc Natl Acad Sci USA 1994; 91:777–781
147. Johnson S, Luu N, Herbst T, Knapp R, Lutz D, Arai A, Rogers G, Lynch G: Synergistic interactions between ampakines and antipsychotic drugs. J Pharmacol Exp Ther 1999; 289:392–397
148. Goff D, Berman I, Posever T, Herz L, Leahy L, Lynch G: A preliminary dose escalation trial of CX516 (Ampakine) added to clozapine in schizophrenia. Schizophr Res 1999; 36:280