Glutamatergic Theories of Schizophrenia

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ABSTRACT

Schizophrenia is a serious mental disorder that affects up to 1% of the population worldwide. Traditional models of schizophrenia have emphasized dopaminergic dysfunction. Over the last 20 years, however, limitations of the dopamine model have become increasingly apparent, necessitating development of alternative models. Glutamatergic models are based upon the observation that the psychotomimetic agents such as phencyclidine (PCP) and ketamine induce psychotic symptoms and neurocognitive disturbances similar to those of schizophrenia by blocking neurotransmission at N-methyl-D-aspartate (NMDA)-type glutamate receptors. Because glutamate/NMDA receptors are located throughout the brain, glutamatergic models predict widespread cortical dysfunction with particular involvement of NMDA receptors throughout the brain. Further, NMDA receptors are located on brain circuits that regulate dopamine release, suggesting that dopaminergic deficits in schizophrenia may also be secondary to underlying glutamatergic dysfunction. Agents that stimulate NMDA receptor-mediated neurotransmission, including glycine-site agonists and glycine transport inhibitors, have shown encouraging results in preclinical studies and are currently undergoing clinical development. Encouraging results have been observed as well with agents such as metabotropic 2/3 agonists that decrease resting glutamate levels, reversing potential disruption in firing patterns within prefrontal cortex and possibly other brain regions. Overall, these findings suggest that glutamatergic theories may lead to new conceptualizations and treatment approaches that would not be possible based upon dopaminergic models alone.

INTRODUCTION

Schizophrenia is a serious mental disorder that affects up to 1% of the population worldwide, and is one of the leading causes of chronic disability. Although causes of schizophrenia remain unknown, the disease has been extensively characterized from both a symptomatic and neurocognitive perspective, and much information has accumulated about elements such as genetic causation and longitudinal course. Although schizophrenia was once seen as a disease affecting only a few key brain regions and regionally discrete neurotransmitter systems such as dopamine, more recent findings implicate widespread cortical and subcortical dysfunction, suggesting more generalized etiology. On a neurochemical level, antagonists of N-methyl-D-aspartate (NMDA)-type glutamate receptors, such as phencyclidine (PCP) or ketamine, uniquely reproduce the symptomatic, neurocognitive and neurochemical aspects of the disorder, suggesting that regardless of underlying etiology, NMDA dysfunction represents a final common pathway leading from pathogenesis to symptoms.

CLINICAL PHENOMENOLOGY OF SCHIZOPHRENIA

Symptoms of schizophrenia are typically divided into three main classes termed positive, negative and cognitive. Positive symptoms consist of such items as suspiciousness/persecution, grandiosity, delusions, and unusual thought content and, in general, reflect features of the schizophrenia experience that are not shared by the general population. Negative symptoms, in con-

Conflict of interest:
Dr. Javitt holds intellectual property rights for use of glycine, D-serine and glycine transport inhibitors in treatment of schizophrenia and related disorders.

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trast, consist of symptoms such as lack of spontaneity, social/emotional withdrawal, poor rapport and blunted affect, and reflect features of normal experience that are reduced in individuals with schizophrenia. Cognitive symptoms – which are also referred to as disorganized symptoms or autistic preoccupation – consist of such elements as conceptual disorganization, disorientation and poor attention. Dopaminergic models of schizophrenia account well only for positive symptoms of the disease. In contrast, glutamatergic models account much more fully for both negative and cognitive symptoms, and thus may serve as an etiological model for the syndrome as a whole.

Another key component of schizophrenia is neurocognitive dysfunction. When tested on basic IQ tests, such as the WAIS, patients with established schizophrenia typically score about 1 standard deviation, or 15 IQ points, below the population mean. Deficits are typically present at first episode and remain relative constant over the course of the illness, suggesting that cognitive decline precedes the onset of substantial symptoms (1, 2). Prospective, follow-back and cross-sectional data all suggest that cognitive functioning may decline during the 3–4 years immediately preceding the onset of schizophrenia symptoms. For example, in one prospective study, poor educational achievement at age 15 was a significant predictor of schizophrenia (3). Two follow-back studies have investigated performance on standardized educational testing (Iowa test) during childhood and adolescence in individuals who subsequently developed schizophrenia. Compared with the general population, such individuals showed only modest deficits even when assessed during 4th and 8th grade, but showed a marked decline in performance between 8th and 11th grade (4, 5).

Similarly, individuals with prodromal schizophrenia who have not yet converted to psychosis show cognitive deficits that are intermediate between those of first-episode and control subjects, and such deficits may predict subsequent conversion to psychosis (6). In a study using the Israeli army database, lower than expected IQ at age 17 – based upon childhood reading and spelling abilities – was a significant risk factor for schizophrenia but not bipolar disorders, such that individuals showing a 10 point or greater discrepancy between expected and actual IQ showed an approximately two-fold elevated risk for developing schizophrenia (7).

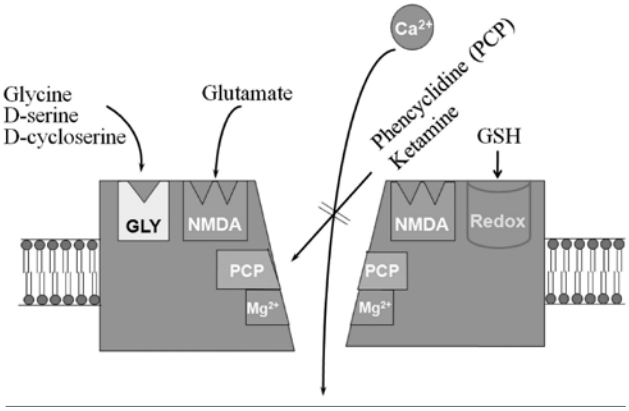
Also based upon findings from the army database, it appears that intellectual performance remains relatively constant between age 17 and subsequent illness onset in individuals who go on to develop schizophrenia, suggesting that most of the cognitive decline occurs premorbidly, although further deterioration in some domains may be observed (8). Overall, these findings highlight neurocognitive dysfunction as a key manifestation of schizophrenia that precedes onset of symptoms, and must therefore be considered central to etiological hypotheses.

NEUROCHEMICAL MODELS OF SCHIZOPHRENIA

The first effective treatments for schizophrenia were discovered fortuitously in the late 1950s, and subsequently shown to mediate their effects at dopamine D2 receptors. Since that time, dopamine has been the primary neurotransmitter implicated in schizophrenia, and the majority of neurochemical studies of schizophrenia continue to focus on dopaminergic mechanisms (9, 10).

Neurochemical models of schizophrenia based upon dopamine have had substantial heuristic value in explaining key symptoms of schizophrenia, in particular, positive symptoms, and in guiding treatment considerations. Nevertheless, significant limitations with regard to the dopamine hypothesis remain. First, no intrinsic deficits have been observed within the dopamine system to account for the presumed hyperdopaminergia associated with schizophrenia. Second, reconceptualizations of the dopamine hypothesis propose that subcortical hyperdopaminergia may coexist with cortical hypodopaminergia, although mechanisms underlying the differential cortical and subcortical abnormalities remain

Figure 1. *Schematic Model of the NMDA Receptor Complex. NMDA=N-methyl-D-aspartate; GLY=glycine, GSH=glutathione.*



to be determined. Finally, dopaminergic dysfunction, in general, accounts poorly for symptom classes in schizophrenia other than positive symptoms and for the pattern of neurocognitive dysfunction associated with schizophrenia. Thus, alternative conceptual models of schizophrenia are required.

An alternative to the dopamine model was first proposed in the early 1990s, based upon the observation that phencyclidine (PCP), ketamine and other similarly acting psychotomimetic compounds induced their unique behavioral effects by blocking neurotransmission at N-methyl-D-aspartate (NMDA)-type glutamate receptors (11, 12) (Figure 1). The ability of these compounds to transiently reproduce key symptoms of schizophrenia by blocking NMDA receptors led to the concept that symptoms in schizophrenia may reflect underlying dysfunction or dysregulation of NMDA receptor-mediated neurotransmission. This model has been increasingly adopted and is now considered to be one of the useful models for both etiological conceptualization of schizophrenia and new treatment development (13-17).

NMDA receptors are composed of a combination of distinct subunits termed NR1, NR2 and NR3. Multiple splice variants of the NR1 subunit have been described, along with multiple subforms of the NR2 subunit termed NR2A-D. All functional NMDA receptors possess one or more NR1 subunits. In addition, most receptors contain a combination of NR2 subunits, with NR2A and NR2B subunits dominating in adult brain. Different combinations of subunits confer different properties to the receptors. It has been suggested that NR2A and NR2B subunit-containing receptors may have differential roles in psychogenesis (18, 19), although others have suggested that combined blockade is needed (20). Because of the lack of subunit specific drugs, it is difficult to determine the involvement of the different subunits types in the pathophysiology of schizophrenia and it remains possible that subtype-selective intervention will prove preferable to generalized modulation across NMDA receptor subtypes.

SYMPTOM PATTERNS FOLLOWING NMDA ANTAGONIST ADMINISTRATION

In initial studies with PCP and ketamine in the early 1960s, researchers noted that both agents produced what would now be considered positive, negative and cognitive symptoms of schizophrenia (12). At the time, however, no formal rating scales were used. Recent studies with ketamine, however, have documented significant increases not only in positive symptoms, but also in negative and cognitive symptoms (21-23). Levels of symptoms during acute ketamine challenge, moreover, tend to show a similar pattern across factors as they do in schizophrenia. When patients with schizophrenia are exposed to ketamine, they also show increases in positive symptoms, as well as negative symptoms (24, 25), suggesting that NMDA antagonists affect a brain system that is already vulnerable in schizophrenia.

COGNITIVE DEFICITS FOLLOWING NMDA ANTAGONIST TREATMENT

As with symptoms, initial studies conducted with PCP in the early 1960s also showed cognitive deficits that are highly reminiscent of schizophrenia (12). Studies conducted with ketamine over the last 15 years have further confirmed and extended these findings. Deficits have been observed across widespread neuropsychological domains including working memory, response inhibition and executive processing (23, 26, 27). Ketamine infusion also reproduces both the severity and type of thought disorder seen in schizophrenia with both, for example, being associated with high levels of poverty of speech, circumstantiality and loss of goal, and relatively low levels of distractive or stilted speech or paraphasias (28). Given the importance of neurocognitive dysfunction to the conceptualization of schizophrenia, these findings support the etiological involvement of NMDA dysfunction in the pathophysiology of schizophrenia.

As opposed to ketamine, administration of dopaminergic agonists such as amphetamine does not reproduce the pattern of deficit observed in schizophrenia. For example, in one recent study that directly compared effects of amphetamine and ketamine in normal volunteers, both ketamine and amphetamine induced positive symptoms and conceptual disorganization. However, only ketamine produced perceptual changes, concrete ideation or negative symptoms. Further, only ketamine induced schizophrenia-like disruptions in delayed recall. Finally, amphetamine did not induce working memory disturbances, and it significantly reversed ketamine-induced disruptions. These findings suggest that augmentation, rather than blockade, of frontal dopaminergic systems may be beneficial in schizophrenia (26). In schizophrenia, amphetamine treatment does not further impair cognition and may in fact lead to cognitive improvement in schizophrenia (29). These findings therefore suggest greater involvement of NMDA than

dopamine receptors in the pathophysiology of cognitive impairment in schizophrenia.

Further evidence for a specific involvement of NMDA receptors in schizophrenia comes from fine-grained analysis of patterns of neurocognitive dysfunction. Neurocognitive deficits in schizophrenia appear generalized when viewed at a "molar" level, such as the level of a cognitive "domain." However, when viewed at a more detailed, "molecular" level, fine-grained differences between different processes do emerge. For example, patients with schizophrenia show reduced ability to learn new information, but intact ability to retain information once it has been learned. This pattern differs from the "amnestic" syndrome that results from bilateral hippocampal damage (2), but is highly similar to effects seen following administration of NMDA antagonists (30). Overall, the pattern of cognitive dysfunction in schizophrenia follows closely the pattern observed following administration of NMDA antagonists across a variety of domains, suggesting that NMDA dysfunction may be seen as a parsimonious model of schizophrenia.

NMDA DYSFUNCTION AND SENSORY PROCESSING IMPAIRMENT

Another key difference between dopaminergic and NMDA models of schizophrenia is predicted involvement of sensory processing. NMDA receptors are widely distributed throughout cortex. In contrast, dopaminergic innervation is much more circumscribed, with relatively sparse innervations of primary sensory cortex (31, 32). An important issue, therefore, is whether information processing deficits in schizophrenia are seen only in higher order cortical regions, such as prefrontal cortex, or if they are observed throughout brain and involve even primary sensory regions. Studies have been performed primarily in auditory and visual systems, although schizophrenia is known to affect other sensory processes such as weight discrimination (33) and other somatosensory processes (34).

Auditory deficits in schizophrenia. Deficits in auditory processing have been investigated using both behavioral and neurophysiological measures. Behaviorally, patients show deficits in matching of tones following brief delay (35), suggesting dysfunction of the auditory sensory memory system. This is a heuristically valuable paradigm, as underlying anatomical substrates have been well characterized in primate and human models. Lesions of auditory sensory cortex, located in superior temporal lobe, produce increases in tone matching threshold without affecting disruptive effects of distracting stimuli. In contrast, lesions of prefrontal cortex increase distractibility without affecting thresholds (36). In patients with schizophrenia, increased thresholds are observed with no accompanying increase in susceptibility to either visual (37) or auditory distraction (38, 39). Further, when equated for performance at short interstimulus interval (<1 s), patients show equivalent decay with increasing interval (39), suggesting normal retention within the sensory memory system. These behavioral findings thus suggest dysfunctional information processing at the level of auditory sensory cortex.

Auditory function in schizophrenia has also been assessed with event-related potentials (ERP). One of the most informative potentials has been mismatch negativity (MMN). MMN is elicited by infrequent changes in nature or pattern of repetitive auditory stimulation. Deviant stimuli may differ from standards in a number of stimulus dimensions, including pitch, duration, intensity or location. Generators for MMN have been mapped to auditory sensory cortex in the region of Heschl's gyrus (40). Deficits in MMN generation were first demonstrated in schizophrenia over 10 years ago and currently represent one of the best replicated neurophysiological findings in schizophrenia (41). Schizophrenia-like deficits in MMN generation can be induced by local infusion of NMDA antagonists into primate auditory cortex (40) and by systemic administration of NMDA antagonists in healthy volunteers (23) , suggesting that such deficits may index NMDA dysfunction at the level of auditory cortex. In contrast, MMN is not modulated via a variety of other psychoactive agents, including the 5-HT2A agonist psilocybin (42) and the D1/D2 agonists bromocriptine and pergolide (43), suggesting relative specificity of the NMDA antagonist psychotomimetic effect.

More recent studies have investigated consequences of elevated tone matching thresholds to more complex forms of information processing dysfunction. Patients with schizophrenia, for example, show well-established deficits in ability to determine emotion based upon vocal modulation (prosody), which are thought to be rate-limiting in terms of functional outcome (44). The etiology of such deficits has been poorly understood, as patients show normal emotional responses to happy or sad events, and show intact internal representation of emotion (45), suggesting that failure to detect emotion may be related to underlying failure to utilize sensory cues.

An initial study of prosodic detection in schizophrenia evaluated the relationship between tone matching performance on the one hand and both auditory and visual emotion detection on the other. Deficits in auditory perceptual performance (tone matching) strongly predicted deficits in auditory, but not visual, emotion detection. Further, although patients showed deficits in both auditory and visual emotion detection, the two sets of deficits were statistically unrelated, suggesting that deficits clustered within, rather than across modalities. These results thus strongly supported the hypothesis that deficits in "social cognition" in schizophrenia, rather than reflecting deficits in the conceptualization of emotion instead reflect upward consequences of the effects of underlying disturbances in underlying tone matching ability (46). A subsequent study demonstrated a similar relationship between tone matching ability and ability to detect attitudinal prosody (sarcasm) (47), as well as non-affective prosody such as ability to differentiate questions from statements (semantic prosody) (48). Further, severity of deficit across individuals correlated highly with reduced structural integrity within auditory white matter pathways at the level of auditory cortex (48). When sensory performance has been evaluated as a function of stimulus properties deficits in emotional detection have been found to involve particularly those types of emotional distinctions that depend upon differentiation of pitch (49). Further, in addition to showing deficits in identifying emotions, patients show deficits in differentiating between emotional intensities, also consistent with inability to process changes in pitch that differentiate emotions (49). Taken together, these findings suggest that basic deficits in NMDA receptor-mediated neurotransmission at the level of auditory sensory cortex lead to sensory level disturbances which, in turn, upward generalize to produce disturbances in high level processes such as ability to interpret tone-of-voice.

Visual processing deficits. Similar studies have now been performed investigating consequences of NMDA dysfunction in the early visual system. The early visual system consists of discrete magnocellular and parvocellular pathways that differ in characteristics and function. The magnocellular pathway provides rapid transmission of low-resolution information to cortex, in order to prime attentional systems and "frame" the overall visual scene. The parvocellular pathway, in contrast, provides slower, higher resolution information to fill in scene details (50). NMDA receptors are located at multiple levels of the early visual system, including retina, lateral geniculate nucleus (LGN) and primary cortex. The magnocellular system, in particular, functions in a non-linear gain mode that is dependent upon NMDA receptor-mediated neurotransmission. Administration of NMDA antagonists to cat LGN produces a characteristic reduction in gain that is also observed in schizophrenia (51).

To date, deficits in visual processing have been demonstrated in schizophrenia using both steady-state (51-53) and transient (54-56) visual evoked potential approaches. Further, deficits in early visual processing produce subsequent impairments on higher order processes such as object identification (57), motion processing (58) and reading (59). Further, change in the physical properties of stimuli to make them more tractable to visual analysis leads to significant improvement in performance in such high-level tasks as the AX-version of the continuous performance task (60) or Wisconsin Card Sorting Test (61). Thus, as in the auditory system, basic deficits in NMDA function within subcortical and cortical systems lead to breakdown of basic sensory discrimination abilities, which, in turn, produce complex patterns of higher level cognitive disturbances in schizophrenia.

GLUTAMATE-DOPAMINE GLUTAMATE-GABA INTERACTIONS

Finally, NMDA dysfunction may also account for both the impaired dopaminergic regulation and the impaired GABAergic neurotransmission that has been documented in schizophrenia. Dopaminergic dysfunction has been studied most extensively using positron emission (PET) or single photon emission (SPECT) markers of response to amphetamine. In such studies, D2 agonists are tagged with appropriate radionuclides (e.g., [^{14}C], [^{123}I]) and pattern of displacement is evaluated following amphetamine administration. Across cohorts, patients with acute schizophrenia show enhanced striatal dopamine release to amphetamine challenge, consistent with presumed dysregulation of subcortical dopamine circuits (62).

Deficits similar to those observed in schizophrenia are observed in normal volunteers undergoing ketamine infusion (63), and in rodents treated subchronically (64, 65) with NMDA receptor antagonists, suggesting that dopaminergic dysregulation in schizophrenia may be "downstream" of a primary deficit in NMDA function. Similarly, NMDA antagonists alter the random firing rate of rodent prefrontal neurons while decreasing burst

firing (66), also supporting the concept that deficits in NMDA transmission may lead to the widely cited disturbances in prefrontal function in schizophrenia.

Changes in GABAergic neurotransmission have also been increasingly well documented over recent years, with studies showing reduced parvalbumin and GAD67 expression, particularly in prefrontal cortex (67-71) and hippocampus (72-74). Similar effects are seen in both rodents (75-79) and monkeys (80) treated with NMDA antagonists such as PCP, as well as in cell culture (81). GABAergic dysfunction in PFC may be directly linked to well-documented deficits in working memory function, and may therefore represent an appropriate target of pharmacological intervention (82). Nevertheless, etiologically such abnormalities may reflect downstream effects of primary deficits in NMDA receptor-mediated neurotransmission.

CLINICAL STUDIES WITH NMDA AGONISTS

Given the ability of NMDA receptor antagonists to induce symptoms that closely resemble those of schizophrenia, a critical issue is whether treatment approaches based upon glutamatergic and NMDA models can lead to new treatment approaches. Over the past decade, several new treatment strategies have been proposed. First, direct and indirect approaches have targeted the glycine modulatory site of the NMDA receptor complex. Direct agonists have included treatment with the naturally occurring amino acids glycine and D-serine, which serve as endogenous modulators of NMDA receptors in vivo, as well the anti-tuberculosis drug D-cycloserine, which fortuitously cross-reacts with the NMDA/glycine site (83). These agents have proven effective in several preclinical models, including reversal of PCP effects in both rodents (84, 85) and primates (86).

Figure 2. *Schematic Model of Synaptic Glycine Regulation by Glycine Transport Inhibitors.*

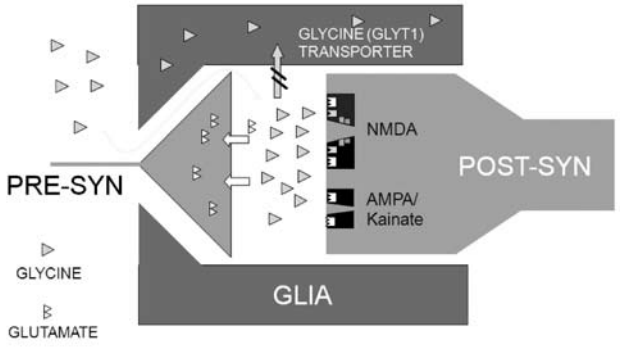


Table 1: *Preclinical Paradigms of Relevance to Schizophrenia in Which Glycine Transport Inhibitors Have Proven Effective*

Test Measure	Reference
Inhibition of phencyclidine (PCP)-induced hyperactivity in vivo	[88, 123, 124]
Inhibition of striatal dopamine release *in vitro*	[125]
Potentiation of hippocampal NMDA responses *in vitro*	[126]
Potentiation of prefrontal/hippocampal NMDA responses *in vitro*	[127-129]
Normalization of prepulse inhibition (PPI) deficits in rodents	[128-130]
Normalization of PCP-induced increases in amphetamine-stimulated dopamine release	[84]
Reversal of locomotor hypersensitivity to amphetamine neonatally PCP-treated rats	[129]
Elevation of CSF glycine levels	[131]

A "second generation" approach to this problem has been the use of glycine type I (GlyT1) transport inhibitors (GTIs). Rather than serving as direct glycine precursors, these compounds increase glycine levels in brain by preventing glycine removal from the synaptic cleft, leading to endogenous increases in CSF glycine levels (87) (Figure 2). An initial study with glycyldodeclamide, a relatively low affinity agent, demonstrated significant reversal of PCP-induced hyperactivity in rodents (88, 89). Since then, high affinity GTIs have been synthesized by several pharmaceutical companies, and have shown to be effective in multiple animal models (Table 1). Several of these compounds are currently in early-stage clinical trials, with results expected over the next several years.

Two other treatment strategies have been proposed. First, in addition to the glycine modulatory site, NMDA receptors contain a redox-sensitive site that is modulated by the oxidized form of glutathione (GSH) (90, 91) (Figure 1). Schizophrenia has also been shown to be associated with reduced levels of GSH (92-94), leading to potential dysfunction of NMDA receptors (95). Early studies testing this mechanism have utilized *N*-acetylcysteine, a glutathione precursor, as a potential psychopharmacological agent.

Second, based upon the observation that NMDA blockade leads to rebound increases in glutamate release that may themselves be pathological (96), it has been proposed that compounds that inhibit presynaptic glutamate release may also be therapeutic (97). Examples of such compounds include the anti-epilepsy drug

lamotrigine and agonists of metabotropic glutamate type 2/3 (mGluR2/3) receptors, which are localized to presynaptic glutamate terminals in prefrontal cortex. mGluR2/3 agonists have been shown to be effective in reversing behavioral effects of NMDA antagonists in rodent models (98), supporting the potential efficacy of these compounds as novel antipsychotic agents. In addition, both lamotrigine (99) and mGluR 2/3 agonists (100) have also been shown to reverse clinical effects of ketamine during acute challenge in normal volunteers, further supporting the applicability of basic models to humans. In general, therefore, as the NMDA model reaches its second decade, the base of treatment development based upon glutamatergic theories continues to increase.

Other metabotropic ligands, including mGluR5 (101, 102) and mGluR8 (103) agonists, have also been proposed as potential treatments for schizophrenia, based upon their ability to modulate NMDA receptor-mediated neurotransmission (104). Finally, N-acetylaspartylglutamate (NAAG) may be an endogenous ligand for mGlu2/3 receptors in CNS. NAAG is broken down by NAAG peptidase (glutamate carboxypeptidase II) (105). Compounds that inhibit NAAG peptidase, such as an experimental inhibitor termed ZJ43, would therefore lead to increased mGlu2/3 occupancy. This compound has been tested preclinically and shown to inhibit PCP- and MK-801-induced behaviors in animals, consistent with an effect on NMDA receptor-mediated neurotransmission (106, 107).

Finally, some authors have suggested that NMDA antagonists may be beneficial, based upon concepts that cognitive deficits in schizophrenia may result from hyper-glutamatergic neurotoxicity (13). Examples of compounds that have been considered based upon this hypothesis are AMPA antagonists and the anti-Alzheimers disease drug memantine. To date, however, clinical experience with NMDA antagonists has not been encouraging (108).

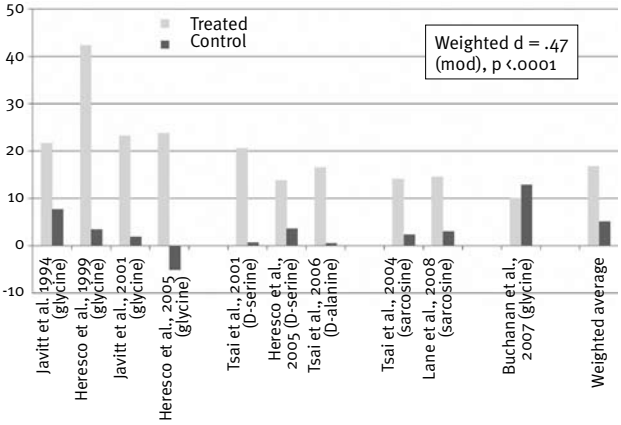
RESULTS OF CLINICAL STUDIES

The most studies to date have been performed with NMDA agonists, primarily because several of the agents used have been natural compounds, and so it has not been necessary to wait for structure activity optimization or preclinical toxicity testing. Nevertheless, this approach is also a limitation, as permeability of these agents may be limited, and delivering optimal doses may therefore be impossible. Nevertheless, positive studies with these compounds have provided proof-of-concept for development of compounds with higher affinity and specificity.

Studies with naturally occurring compounds to date have primarily used glycine, administered at a dose of up to 800 mg/kg (approx. 60 g/d) (109-112); D-serine, administered at a dose of 30 mg/kg (approx. 2.1 g/d) (113, 114) or D-alanine administered at a dose of 100 mg/kg (115); and sarcosine, administered at a dose of 30 mg/kg (approx. 2.1 g/d) (116, 117). For glycine, this represents the highest practical dose because of the quantity of amino acid needed to significantly increase brain glycine levels. For other compounds, formal dose findings studies have not been performed, and maximum tolerated doses are presently unknown.

Across all studies utilizing full agonists in combination with either typical or newer atypical antipsychotic drugs, NMDA agonists have been found to produce an approximately 15% improvement in negative symptoms, along with significant changes in positive and cognitive symptoms in some but not all studies (83) (see Figure 3). One study has evaluated effects of glycine in a limited number of individuals showing prodromal symptoms of schizophrenia. In that study, large effect-size improvement was observed, including early remission in three of 10 subjects (118). These data, if confirmed, would indicate that NMDA agonists might have a primary role in the earliest stages of schizophrenia psychosis, with potential impact across symptomatic domains.

Figure 3. *Summary of clinical trials performed to date with full NMDA agonists combined with antipsychotics other than clozapine. Studies were conducted using the amino acid glycine at doses of 0.4-0.8 g/kg (30-60 g/d) unless otherwise indicated. Further details about individual studies are provided in (83). CONSIST refers to The Cognitive and Negative Symptoms in Schizophrenia Trial (132). Statistics were calculated as weighted average of % change scores for negative symptoms, across trials.*



Studies of other mechanisms also show suggestive findings. Thus, one study of N-acetylcysteine, a precursor of glutathione, produced significant improvement in PANSS total and negative symptoms in schizophrenia (119), along with improvement in generation of MMN, which may serve as a biomarker of NMDA dysfunction (120). Two small studies with lamotrigine showed suggestive results (121, 122), although a subsequent multicenter double-blind study was negative. To date, one phase II study with the oral mGluR2/3 agonist prodrug LY2140023, used as monotherapy in acutely relapsing subjects, showed clinical efficacy similar to that of olanzapine with markedly reduced incidence of metabolic side effects. Although this study requires replication, it is encouraging with regard to overall efficacy of glutamatergic approaches.

SUMMARY

Glutamatergic models of schizophrenia were first proposed over two decades ago, based upon the effects of the agents PCP and ketamine, which were shown to induce their unique psychotomimetic effects by blocking neurotransmission at NMDA-type glutamate receptors. Since that time, glutamatergic models have been strongly supported by NMDA antagonists studies in animals, as well as ketamine challenge studies in humans. Over that time, potential molecular contributors to NMDA dysfunction have been increasingly documented. New treatment approaches based upon glutamatergic approaches are only now reaching the clinic, and will serve to further elucidate and refine these models over upcoming years. Whether glutamatergic approaches will eventually supplant dopamine antagonists for treatment of positive symptoms remains to be determined. Nevertheless, glutamatergic approaches offer particular hope for treatment of negative symptoms and cognitive deficits in schizophrenia, and thus for improvement of the clinical situation of thousands of patients in Israel and millions of patients worldwide.

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