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ORIGINAL PAPER

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Potentiation of the NMDA receptor in the treatment of schizophrenia: focused on the glycine site

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Abstract *N*-methyl-D-aspartate receptor (NMDAR) hypo-function theory of schizophrenia proposes that impairment in NMDAR function be associated with the pathophysiology of schizophrenia and suggests that enhancement of the receptor function may produce efficacy for schizophrenia. Consistent with this theory, for the last decade, clinical trials have demonstrated that the enhancement of NMDAR function by potentiating the glycine site of the receptor is efficacious in the treatment of schizophrenia. Full agonists of the glycine site, glycine and D-serine and a glycine transporter-1 inhibitor, sarcosine, added to antipsychotic drugs, have been shown to be effective in the treatment of negative symptoms and possibly cognitive symptoms without significantly affecting the positive symptoms of schizophrenia. A partial agonist of the glycine site, D-cycloserine, added to antipsychotic drugs, can be effective for the negative symptoms at the therapeutic doses. However, these drugs have not shown clinical efficacy when added to clozapine, suggesting that the interactions of clozapine and the glycine site potentiators may be different from those of other antipsychotic drugs and the potentiators. This article suggests that the glycine site potentiators may produce efficacy for negative and cognitive symptoms by blocking apoptosis-like neuropathological processes in patients with chronic schizophrenia and thereby can deter progressive deterioration of the disorder. This article proposes a polypharmacy of glycine site potentiators augmented with antipsychotic drugs to control positive and negative symptoms in a synergistic manner and block deterioration in schizophrenia. Since the NMDAR complex consists of multiple sites modulating receptor functions, the efficacy of glycine site potentiators for schizophrenia suggests the possibility that manipulation of other modulating sites of the NMDAR can also be efficacious in the treatment of schizophrenia.

Key words glycine site agonists · NMDA receptor · negative symptoms · cognitive symptoms · neurodegeneration · schizophrenia

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Introduction

The clinical trials of agents enhancing NMDAR function as potential therapeutic drugs for schizophrenia are relatively new. The theoretical basis for the efficacy of agents enhancing NMDAR function for schizophrenia primarily derives from the glutamatergic dysfunction theories of schizophrenia [32, 65, 91]. The most compelling evidence for glutamate dysfunction in schizophrenia stems from clinical observations that phencyclidine (PCP) and ketamine, non-competitive NMDAR antagonists, can induce a wide range of schizophrenic symptoms including positive, negative and cognitive symptoms in healthy individuals [19, 72, 109]. Competitive NMDAR antagonists and the antagonists at the glycine site, a

positive modulatory site, of the NMDAR can also induce psychotomimetic states resembling schizophrenia [10, 18, 76]. In rodents, unique behaviors such as hyperlocomotion and characteristic stereotypic behaviors, which could be considered to be equivalent to the positive symptoms of schizophrenia, and social isolation and reduced sexual interactions, which could be considered to be equivalent to the negative symptoms of schizophrenia, have been observed after the administration of non-competitive NMDAR antagonists, PCP, ketamine, MK-801 and competitive NMDAR antagonists [50, 83, 102]. These characteristic behavioral disturbances are also observed in mice with defects in NMDAR expression [84]. Thus, these lines of evidence together suggest that a NMDAR deficit can be associated with the pathophysiology of schizophrenia. The other line of evidence supporting the NMDAR hypofunction theory in schizophrenia derives from postmortem studies, which have reported defects in the NMDAR and/or glutamate receptor-mediated transmission such as disturbances in the density of NMDAR and non-NMDARs or reduced presynaptic release of glutamate in the brains of schizophrenic patients [71].

The NMDAR has a glutamate recognition site to which competitive NMDAR agonists, glutamate, D-aspartate and NMDA bind to activate the receptor. The strychnine-insensitive, glycine binding site is a positive modulatory site for the receptor [60, 70]. Occupation of the glycine site is required so that agonists at the glutamate-binding site can activate the receptor and open the cation channel [18]. Thus, glycine agonists are called "co-agonists" of the NMDAR. Glycine and D-serine are full agonists at the glycine site and D-cycloserine is a partial agonist at the site [51, 92]. *N*-methyl glycine (sarcosine) is a glycine transporter-1 inhibitor, which potentiates the glycine site by increasing the concentration of glycine at the glycine site of the receptor [113]. Since direct stimulation of the glutamate-binding site of NMDARs can produce excitotoxic neuronal death, attention has been paid to the potentiation of the glycine site of NMDAR to attempt to enhance NMDAR function while avoiding direct stimulation of NMDARs [73, 98]. Although dysfunction of the NMDAR and other glutamatergic receptors in schizophrenia has been discussed for over two decades, clinical trials to explore the efficacy of drugs potentiating NMDAR function for schizophrenia are at an early stage. This article will summarize data on the efficacy of the potentiators of the glycine site including full glycine agonists, glycine, milacemide and D-serine, a partial glycine agonist, D-cycloserine and a glycine transporter-1 inhibitor, sarcosine, in the treatment of chronic schizophrenia and discuss several critical issues as follows: the efficacy of the augmentation of glycine receptor potentiators to antipsychotic drugs for the treatment of negative and cognitive symptoms; the efficacy of the augmentation of the glycine receptor potentiators to clozapine; the possible role of glycine receptor potentiators in deterring the deterioration of schizophrenia; the combination of glycine receptor potentiators and antipsychotic drugs as a novel therapeutic strategy in the treatment of schizophrenia.

Efficacy of full glycine agonists in treatment of schizophrenia

Glycine

Waziri [122] first reported that glycine improved psychotic symptoms and psychosocial functions in a 9 month naturalistic follow-up of patients with chronic-schizophrenia (Table 1). Costa et al. [12] reported from an open label trial that a low dose of glycine (15 mg/day) added to conventional antipsychotic drugs reduced psychotic symptoms in some patients with chronic schizophrenia. Potkin et al. [93] reported that a low dose of glycine (15 mg/day) added to conventional antipsychotic drugs improved global clinical state, but did not improve psychotic symptoms in patients with chronic schizophrenia, who poorly responded to antipsychotic drugs in a placebo-controlled, double-blind trial. Javitt and his colleagues have conducted a series of placebo-controlled, double-blind, glycine augmentation trials [44, 46, 47, 49, 56, 77]. Javitt et al. [56] have first reported that low dose glycine (30 mg/day) added to conventional antipsychotic drugs markedly reduced negative symptoms in patients with chronic schizophrenia without significant effects on positive symptoms and general psychopathology. These findings have been confirmed by a series of well controlled augmentation studies of high dose glycine (60 g/day), which have consistently reported that glycine augmentation clearly improved negative symptoms [46, 47, 77] and could improve cognitive symptoms [47] in patients with chronic schizophrenia, which poorly responded or were resistant to medication treatment. In recent, Heresco-Levy and Javitt [44] reported that glycine (60 g/day) added to conventional and atypical antipsychotic drugs improved negative and positive symptoms and general psychopathology in patients with treatment-resistant schizophrenia in a placebo-controlled, double-blind trial.

Milacemide

Milacemide is an acetylated "prodrug" of glycine, which converts into glycine through deacetylation [87] (Table 1). Rosse et al. [100, 101] have shown that a low dose of milacemide (0.4 g/day) did not improve psychotic symptoms, and a high daily dose (1.2 g/day) worsened schizophrenic symptoms in drug-free patients with schizophrenia in 2 open label trials. This

Table 1 Antipsychotic effects of glycine site potentiators

Clinical trials	Sample size	Trial design	Duration of trials (weeks)	Daily doses	Antipsychotic drugs	Rating scales	Outcome
Glycine							
Waziri (1988) [122]	11	open label, naturalistic	8–9 months	5–25 g	drug-free	clinical observations	⇑ psychotic/ psychosocial
Costa et al. (1990) [12]	6	open label	5	15 g	conventional	BPRS	⇑
Potkin et al. (1992) [93]	18	double-blind, placebo-controlled	6	15 g	conventional	CGI, SANS, BPRS	⇑ BPRS
Javitt et al. (1994) [56]	14	double-blind, placebo-controlled	8	30 g	conventional	PANSS	⇑ –
Liederman et al. (1996) [77]	5	open label	8	60 g	conventional/atypical	PANSS/SANS	⇑ –
Heresco-Levy et al. (1996) [46, 49]	11	double-blind, placebo-controlled	6	60 g	conventional/atypical	PANSS/BPRS	⇑ –
Heresco-Levy et al. (1999) [47]	22	double-blind, placebo-controlled	6	60 g	conventional/atypical	PANSS/BPRS	⇑ –
Milacemide							
Rosse et al. (1990) [101]	5	open label	5	1.2 g	drug-free	SANS/BPRS/CGI	⇓ –
Rosse et al. (1991) [100]	4	open label	4	400 mg	drug-free	SANS/BPRS/CGI	⇔
Tamminga et al. (1992) [111]	6	double-blind, placebo-controlled	6	1.2 g	drug-free	BPRS	⇔
D-serine							
Tsai et al. (1998) [116]	28	double-blind, placebo-controlled	6	30 mg/kg	conventional	PANSS, SANS, CGI, WCST, Ham-D	⇑ cognitive
D-alanine							
Tsai et al. (2005)	32	double-blind, placebo-controlled	6		conventional	PANSS, SANS, CGI	⇑ –/+ ⇑ –
D-Cycloserine							
Simeon et al. (1970) [108]	10	case report	18–111 days	1–3 g	drug-free	clinical observations	⇓
Cascella et al. (1994) [9]	7	open label	6	250 mg	conventional	CGI, SANS, BPRS	⇓–/+/gen psychopath
Goff et al. (1995) [36]	9	single blind	2	5, 15, 50, 250 mg	conventional	SANS, BPRS	⇓– at daily 50 mg
Rosse et al. (1996) [99]	13	double-blind, placebo-controlled	4	10, 30 mg	molindone	SANS, BPRS, CGI	⇔
van Berkel et al. (1996) [5]	7	single blind	20 days	5, 15, 50, 100, 250 mg	conventional	PANSS, CGI	⇑ – at daily 100 mg
van Berkel et al. (1999) [4]	25	double-blind, placebo-controlled	8	100 mg	conventional	PANSS, CGI	⇔ – ⇓ + / gen psychopath
Goff et al. (1999) [35]	39	double-blind, placebo-controlled	8	50 mg	conventional	PANSS, SANS, GAS *cognitive tests, Ham-D	⇑ –
Heresco-Levy et al. (2002) [43]	16	double-blind, placebo-controlled	6		conventional/atypical	PANSS, SANS, Ham-D	⇑ –
Duncan et al. (2004) [21]	22	double-blind, placebo-controlled	4	50 mg	conventional	PANSS, SANS, BPRS *cognitive tests	⇔ –/+ /cognitive
Goff et al. (2005) [34]	26	double-blind, placebo-controlled	6 months	50 mg	conventional	PANSS, SANS, BPRS *cognitive tests	⇔ –/+ / cognitive
N-methylglycine (sarcosine)							
Tsai et al. (2004) [114]	38	double-blind, placebo-controlled	6	2 g	conventional/risperidone	PANSS, SANS, Ham-D	⇑ all
Lane et al. (2006) [74]	65	double-blind, placebo-controlled	6	2 g sarcosine 2 g D-serine	risperidone risperidone	PANSS, SANS PANSS, SANS	⇑ all ⇑ all

Rating Scales: PANSS—positive and negative syndrome scale, SANS—scale for the assessment of negative symptoms, BPRS—brief psychiatric rating scale, CGI—clinical global impression, GAS—global assessment scale, Ham-D—hamilton rating scale for depression, WCST—wisconsin card sorting task, *Abrams and Tayler rating scale, Sternbery memory/continuous performance, Symptoms outcomes: – —negative, + —positive, gen psychopath, general psychopathology, all, –/+ / cognitive/general psychopathology, ⇑—improved, ⇓—exacerbated, ⇔—not improved

effect is in line with a clinical trial of milacemide by Tamminga et al. [111], who showed no efficacy of high dose milacemide (1.2 g/day) in drug-free patients with schizophrenia in a placebo-controlled, double-blind trial. These clinical trials were preliminary trials with a small number of patients and short trial periods. Well-designed trials with a substantial number of patients are needed to examine the therapeutic potential of milacemide.

D-serine

D-serine is a full glycine agonist, which is synthesized and stored in astrocytes. Presynaptic glutamate release triggers the release of D-serine from astrocytes to co-activate the NMDAR with glutamate [103] (Table 1). Thus, it has been proposed that D-serine be a putative non-classical neurotransmitter of NMDAR [64]. Tsai et al. [116, 117] reported that D-serine (30 mg/kg) added to conventional antipsychotic drugs improved negative, positive and general psychopathology in placebo-controlled, double-blind trials. This study also showed that D-serine improved cognitive function associated with the frontal cortical functions in patients with chronic treatment-resistant schizophrenia with primary deficit syndrome [67]. These findings basically concur with a recent trial, which reported that D-serine (30 mg/kg) added to olanzapine or risperidone reduced the negative, cognitive and depressive symptoms of treatment-resistant schizophrenia [45].

D-alanine

Tsai et al. [115] reported from a double-blind, placebo-controlled trial that D-alanine, a full glycine agonist, (100 mg/kg) added to conventional antipsychotic drugs improved negative and positive symptoms and general psychopathology in patients with treatment-resistant schizophrenia and prominent deficit symptoms (Table 1).

Efficacy of D-cycloserine, a partial glycine agonist, in treatment of schizophrenia

Simeon et al. [108] observed in a case report that D-cycloserine worsened psychosis in drug-free psychotic patients. Cascella et al. [9] reported that a high dose of D-cycloserine (250 mg/kg daily) added to conventional antipsychotic drugs worsened psychotic symptoms in patients with chronic schizophrenia in an open label trial (Table 1). Rosse et al. [99] reported that 10 mg or 30 mg/day of D-cycloserine added to molindone did not improve schizophrenic symptoms in drug-free patients with schizophrenia in a placebo-controlled, double-blind trial. van Berckel et al. [5] reported that D-cycloserine only at 100 mg daily, but not at 15, 25, 50, or 250 mg daily, reduced negative symptoms, but failed to change other symptoms in drug-free patients with schizophrenia. D-cycloserine at other doses failed to improve any symptoms in these patients. van Berckel et al. [4] reported that D-cycloserine (100 mg/kg) added to conventional antipsychotic drugs worsened positive symptoms and general psychopathology in a placebo-controlled, double-blind trial.

Goff et al. [36] conducted a placebo controlled, dose-finding trial of D-cycloserine. In this study, the authors conducted a single blind trial of 5, 15, 50, and 250 mg daily of D-cycloserine added to conventional antipsychotic drugs in patients with chronic schizophrenia with prominent negative symptoms (Table 1). They reported that only 50 mg daily D-cycloserine reduced negative symptoms and improved reaction time as measured by Sternberg's Item Recognition Paradigm, a test mediated in part by the prefrontal cortex. This study reported no significant changes in psychotic symptoms.

These findings were generally confirmed by the expanded placebo-controlled, double blind studies of 50 mg/day of D-cycloserine added to conventional or atypical antipsychotic drugs with patients who were screened to meet the criteria of the primary deficit syndrome or treatment-resistant schizophrenia [35, 43, 44, 48]. These trials have reported that D-cycloserine added to conventional or atypical antipsychotic drugs reduced negative symptoms selectively.

However, recent placebo-controlled, double-blind trials have shown that D-cycloserine (50 mg/day) did not reduce negative, positive and cognitive symptoms of schizophrenia [21, 34]. At this point, it is controversial whether the "therapeutic dose" of D-cycloserine (50 mg/day) is efficacious in the treatment of schizophrenia.

Efficacy of sarcosine, a glycine transporter-1 inhibitor, in treatment of schizophrenia

Sarcosine, a glycine transporter-1 inhibitor, plays a pivotal role in the activation of the glycine site of the NMDAR by saturating the concentration of glycine within synaptic clefts [6, 54] (Table 1). Recent studies have shown in placebo-controlled, double-blind trials that sarcosine (2 g/day) added to conventional antipsychotic drugs or risperidone improved the positive, negative, and depressive symptoms and general psychopathology of schizophrenia in patients with stabilized chronic schizophrenia [114] and in inpatients with acute exacerbations of schizophrenia [74]. These findings on the efficacy of sarcosine appear to be consistent with those of full glycine agonists in that glycine site potentiators added to antipsychotic drugs can improve negative and cognitive symptoms and general psychopathological

symptoms, but may not improve these symptoms when added to clozapine.

Efficacy of glycine agonists for negative symptoms of schizophrenia

The most salient and consistent finding in the clinical trials of glycine site potentiators is that these drugs ameliorate the negative symptoms of schizophrenia. Full glycine agonists, glycine, D-serine and D-alanine, and a glycine transporter-1 inhibitor, sarcosine, consistently improve negative symptoms. It has not been fully verified whether D-cycloserine at therapeutic doses improves schizophrenic symptoms. Up to date, there has been no double blind, placebo-controlled trial which reported that glycine potentiators worsen schizophrenic symptoms except for D-cycloserine, which can aggravate schizophrenic symptoms at high doses [4, 9]. The negative symptoms of schizophrenia are grouped into two types: primary and secondary negative symptoms. Primary negative symptoms are enduring negative symptoms innate in schizophrenia and are known to poorly respond to antipsychotic drug treatment [14, 68]. On the other hand, secondary negative symptoms occur as the consequences of various factors including positive symptoms, the side effects of medications, depression, and environmental deprivation [30]. Treatment of positive symptoms and the adverse effects of medications, psychosocial treatments and social support are shown to improve secondary negative symptoms, but not necessarily primary negative symptoms [53]. In this context, an important question is raised: Do glycine site potentiators improve primary negative symptoms? At this point, there is no clear answer available because most clinical trials of glycine site potentiators have not specifically differentiated primary and secondary negative symptoms. However, the review of the data suggests that glycine site potentiators are likely to improve primary negative symptoms. Most subjects recruited for trials of glycine site potentiators were patients with chronic schizophrenia with prominent negative symptoms, who responded to antipsychotic drugs poorly and exhibited deficit syndrome [26, 33, 36, 44, 45, 47, 48, 116]. These clinical profiles of subjects recruited for the studies imply that many of these patients may have primary negative symptoms. In some studies, subjects with depressive symptoms, extrapyramidal side effects or a short period of negative symptoms were excluded from the trials [114]. Furthermore, Tsai et al. [116, 117] and Goff et al. [33] have recruited subjects with chronic schizophrenia and prominent negative symptoms, which met the diagnostic criteria of the Scale for Deficit Symptoms for Primary Negative Symptoms [67]. They have shown a marked reduction in negative symptoms in these subjects. Thus, although there is no conclusive evidence, all these data together strongly suggest that glycine site potentiators can improve the primary negative symptoms of schizophrenia.

Whether glycine site potentiators improve secondary negative symptoms is unclear. It is possible that glycine site potentiators improve secondary negative symptoms by ameliorating positive symptoms and/or the adverse effects of antipsychotic drugs. However, this possibility is not likely because most of the trials of glycine site potentiators added to antipsychotic drugs have reported that glycine did not improve positive symptoms or extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) [33, 47, 74, 114, 116, 117]. Trials of glycine agonists with drug-free schizophrenic patients, who may have more prominent positive symptoms than patients stabilized by antipsychotic drugs, have shown that milacemide did not improve or aggravate positive symptoms [100, 101, 111]. These data suggest that glycine agonists may not significantly improve secondary negative symptoms. Thus, the efficacy of glycine site potentiators for negative symptoms is more likely to derive from their efficacy for primary negative symptoms.

Efficacy of glycine site potentiators for cognitive symptoms of schizophrenia

The cognitive deficits of schizophrenia encompass a variety of cognitive functions such as intellectual decline, deficits of working memory, executive functions and impaired attention. Numerous preclinical studies have shown that NMDAR-mediated transmission is a major cellular basis for memory and learning [96]. A large body of evidence indicates that potentiation of the NMDAR via stimulating the glycine site improves cognitive functions. For example, D-cycloserine improves visual recognition memory, spatial memory in animals and attenuates deficits in working memory in animals [3, 105, 112]. One recent study showed that a high dose of glycine enhanced working memory and attention in healthy adults [28]. Cognitive deficits observed in psychosis induced by PCP and ketamine mimic cognitive deficits in schizophrenia. Thus, impairments in alertness and attention span, the registration and recall of working memory, and executive functions have been observed by ketamine and PCP as a part of NMDAR antagonist-induced psychosis in healthy adults [71, 72]. In this context, an important question is whether the potentiation of NMDAR function improves cognitive deficits in schizophrenia? To date, trials of full glycine agonists have consistently shown that glycine [46, 47], D-serine [45, 116] and D-alanine [115] added to antipsychotic drugs improved cognitive symptoms as assessed by the cognitive subscales of positive and negative syndrome (PANSS). Tsai et al. [116] also reported that D-serine added to conventional antipsychotic drugs improved cognitive functions associated with prefrontal cortical function assessed by wisconsin card

Table 2 Effects of glycine site potentiators added to clozapine

Clinical trials	Sample size	Duration of trials (weeks)	Daily doses	Rating scales	Outcome
Glycine					
Potkin et al. (1999) [94]	19	12	30 g	SANS, BPRS	not efficacious
Evins et al. (2000) [26]	27	8	60 g	PANSS, SANS, BPRS	not efficacious
D-serine					
Tsai et al. (1999) [117]	20	6	30 mg/kg	PANSS, SANS, CGI, WCST	not efficacious
D-Cycloserine					
Goff et al. (1996) [37]	10	8	5, 15, 50, 250 mg	SANS, BPRS	not efficacious
Goff et al. (1999) [33, 35]	17	6	50 mg	PANSS, SANS, GAS *cognitive tests, Ham-D	negative symptoms exacerbated

All are double-blind, placebo-controlled
*Abrams and Tayler rating scale, Sternbery Memory/Continuous Performance

sorting test (WCST). Sarcosine has also been shown to improve cognitive symptoms in PANSS [74, 114]. In contrast, the efficacy of D-cycloserine on cognitive symptoms has not yet been clearly demonstrated. Goff et al. [36] reported that D-cycloserine, 50 mg daily added to conventional antipsychotic drugs improved cognitive function as measured by Sternberg's Item Recognition Paradigm (SIRP), a neuropsychological battery designed to test working memory [36]. However, other trials have shown no efficacy of D-cycloserine (50 mg/day) added to antipsychotic drugs on cognitive symptoms including cognitive symptoms related to the function of the prefrontal cortex in schizophrenic patients [21, 34, 43]. These trials together suggest that full glycine agonists and a glycine transporter-1 inhibitor, sarcosine, can improve cognitive symptoms, but a partial glycine agonist, D-cycloserine, may not have effects on the negative symptoms of schizophrenia (Table 1).

Do glycine agonists improve negative symptoms when added to clozapine?

Interestingly, recent clinical trials have shown that glycine agonists added to clozapine, as opposed to the agonists in combination with other antipsychotic agents, did not show efficacy for schizophrenia (Table 2). Recent studies have reported that glycine added to clozapine did not affect the negative and positive symptoms and general psychopathology of schizophrenia [26, 94]. Tsai et al. [117] also reported that D-serine added to clozapine did not improve schizophrenic symptoms. Goff [33, 37] have also reported that 50 mg daily of D-cycloserine, added to clozapine, worsened negative symptoms, while not affecting other psychopathologies of schizophrenia. A recent placebo-controlled, double-blind study reported that sarcosine (2 g/day) added to clozapine did not affect the positive, negative, and depressive symptoms and general psychopathology in patients with schizophrenia [74]. These unexpected findings suggest that the manner in which glycine site potentiators interact with clozapine may differ from their interactions with other antipsychotic agents. In fact, there has been a substantial body of evidence that clozapine enhances NMDAR transmission. Differing from conventional antipsychotic drugs, clozapine increases glutamate release [124], potentiates NMDA transmission [1], prevents electrophysiological responses to NMDAR antagonists [120] and reverses phencyclidine-induced neuronal excitability in the prefrontal cortex [2] and blocks NMDAR antagonist-induced metabolic activation [20] and behavioral disturbances [11]. These data together suggest that clozapine may increase NMDAR-mediated glutamate transmission in diverse ways [120] so that further enhancing NMDAR transmission by potentiating the glycine site may not be significant. This hypothesis may account for clinical observations that the administration of clozapine improved the negative symptoms [106], but glycine agonists added to clozapine did not improve the negative symptoms further.

Mechanism of action of glycine site potentiators in treatment of schizophrenia

It has been proposed that the NMDAR antagonist model of schizophrenia is associated with a striatal hyperdopaminergic state [75]. Animal studies have reported that a single administration of PCP and MK 801, the noncompetitive NMDAR antagonists, induces a striatal hyperdopaminergic state which increased dopamine (DA) neuron activity of the striatal dopamine system, increased dopamine release at the neuronal terminals of the system [110] and exhibited an increase in dopamine release in the nucleus accumbens and the striatum [57, 59, 110]. Human neuroimaging studies have shown that a single administration of ketamine increases DA release to the same magnitude as amphetamine does at the ventral striatum [7, 119], and enhances an amphetamine-induced increase in striatal DA release in humans [63]. These animal and human studies suggest that a striatal hyperdopaminergic state accounts for NMDAR antagonist-induced psychosis resembling schizophrenia, compatible with the dopamine theory of schizophrenia. However, a NMDAR antagonists-

induced acute hyperdopaminergic state is followed by a hypodopaminergic state as demonstrated by a decrease in the utilization and release of DA in the prefrontal cortex and the striatum in animals [57–59]. Brain imaging studies have shown that acute treatment with PCP increased extracellular levels of dopamine in the striatum [104], but a chronic treatment with PCP decreased the extracellular level of dopamine in the brains of primates [118]. Animal studies have shown that NMDAR antagonist-induced changes in psychomotor activity are not totally dependent on the dopaminergic state. For example, unique psychomotor activities induced by NMDAR antagonists are not modified by DA_2 receptor antagonists, but occur in sustained hyperdopaminergic states in animals. This pyschomotor activity also occurs in monoamine depleted animals [8, 83]. These suggest that NMDA antagonist-induced psychosis cannot be accounted for only by a hyperdopaminergic state. Other pathophysiological processes triggered by the blockade of NMDARs are associated with NMDAR antagonist-induced psychotic features.

The mechanism by which the blockade of NMDAR leads to schizophrenia-like psychosis is not well understood. A large body of evidence indicates that NMDAR antagonists produce toxic neuronal injury [23, 80]. A single administration of NMDAR antagonists induces largely reversible neuronal damages in limbic forebrain [89, 90]. Repeated administration of NMDAR antagonists, however, induces diverse pathological changes from the reversible morphological changes of neurons such as vacuolization to apoptosis-like neuronal cell death in limbic structures [22, 24, 29]. These sublethal cellular changes are generally subtle, and apoptosis-like neuronal death is usually not accompanied by gliosis [22, 24, 29]. NMDAR antagonist-induced neuronal injuries in animals and the psychotomimetic effect of the drugs in humans occur at similar developmental ages. The systemic administration of MK-801 did not induce neurotoxic injury in rodents until the age of puberty, and increasingly induced the lesions with age until early adulthood [27, 29]. A similar age dependency was observed in the psychotomimetic properties of NMDAR antagonists [40, 95]. In humans, the onset of schizophrenia is rare until puberty, and increases dramatically in young adults [97]. In addition, unique animal behavioral disturbances induced by NMDAR antagonists were also observed in animals with genetic deficits of the NMDAR [83, 84]. Recent postmortem studies have shown diverse changes of neuronal atrophy such as reduced cell size, the loss of dendrites and synapses, and neuronal death in the prefrontal lobe, limbic cortex and hippocampus [38, 41]. One of the most consistent postmortem findings is the lack of significant gliosis, suggesting that these neuropathological changes may not be the "classical" type of neurodegeneration accompanied by gliosis [41]. These pathological changes are consistent with a progressive enlargement of the ventricles and the loss of cortical gray matter as shown in brain imaging studies [15, 39, 62, 79]. This pathomorphology is more closely associated with schizophrenic patients who have cognitive impairment and deterioration [15]. In recent, these neuropathological changes have been explained by altered neuronal apoptosis (program cell death), which produces various neuropathologies from neuronal atrophy, decreased neuropil, dendritic atrophy to neuronal death without active gliosis [52]. In this context, NMDAR antagonist-induced neuronal injury could be a viable model in investigating the neuropathology of schizophrenia. Glycine site potentiators can block neuropathological processes in schizophrenia as neuroprotective drugs, and thereby produce efficacy for negative and cognitive symptoms.

Can glycine site potentiators deter deterioration in schizophrenia?

Schizophrenia is known to take a deteriorating course. Longitudinal follow-up studies indicate that progressive deterioration in schizophrenia is predominantly reflected in primary negative and cognitive symptoms [78, 79, 82]. Thus, these symptoms are less common and less severe in the early stages of the disorder, not necessarily worsened in acute exacerbations, but more likely to be more persisting and prominently manifested as the disorder progresses [82, 123]. Clinical trials have shown that some atypical antipsychotic drugs such as clozapine and olanzapine are effective in the treatment of negative symptoms [61, 66]. Still, it remains unclear whether these drugs treat primary negative symptoms directly or secondary negative symptoms of the disorder primarily by treating positive symptoms and producing less adverse effects such as is the case with atypical antipsychotic drugs [53, 85]. Again, it remains unclear whether antipsychotic drugs are effective for the primary negative symptoms [25, 68, 69]. It is controversial whether antipsychotic drugs can slow down the deteriorating course of schizophrenia [42]. Brain imaging studies have shown progressive reductions in the volume of the cortical gray matter and increases in the volume of the ventricles after the onset of illness in some schizophrenic patients [15, 17, 39, 79, 107]. These findings are associated with chronic treatment of refractory schizophrenic patients with prominent negative symptoms and poor outcome, suggesting that progressive brain atrophy might be associated with clinical deterioration in schizophrenia [39]. Recent postmortem studies have shown the atrophy of neurons, loss of neuronal processes and synapses in the cortex and reduced cortical volume in schizophrenic patients [38]. Thus, although it is far from conclusive, evidence taken together from clinical follow-ups, brain imaging and postmortem studies

Table 3 Glycine site potentiators and antipsychotic drugs in treatment of schizophrenia

	Glycine site potentiators	Antipsychotic drugs
Model of psychopathology	PCP model (NMDAR hypofunction theory)	Amphetamine model (dopamine theory)
Primary mechanism of action	Potentiation of NMDA receptor	Blockade of dopamine receptor
Major efficacy	Negative symptoms	Positive symptoms
Augmentation to clozapine	Loss of efficacy	Efficacious
Onset of action	<2 weeks	3–4 weeks

suggests that a "non-classical" progressive neurodegeneration may occur in chronic schizophrenic patients with prominent negative symptoms [52]. The NMDAR hypofunction theory of schizophrenia proposes that a diminished function of NMDARs can produce sublethal and lethal neuronal injury including apoptosis-like neuronal death in schizophrenic patients [13, 23, 88]. This suggests that diminished NMDAR function can contribute to apoptosis-like neuropathology, not necessarily accompanied by gliosis in schizophrenia [13]. This model is consistent with clinical observations that glycine site potentiators ameliorate the negative symptoms and possibly cognitive symptoms of schizophrenia, which reflect deterioration of the disorder [82, 123]. This suggests the possibility that a long-term enhancement of NMDAR function by glycine site potentiators could slow down clinical deterioration in schizophrenia. At this point, whether glycine agonists and glycine transporter inhibitors actually deter deterioration in schizophrenia remains to be studied. Most glycine trials have been conducted for short periods of trial time (from 2 to 8 weeks). The development of neuropathology in schizophrenia might be a slow and gradual process. Thus, well-controlled, long-term trials of glycine site potentiators are required to address the efficacy of these drugs in attenuating clinical deterioration in schizophrenia.

Complementary effects of glycine site potentiators and dopamine blocking antipsychotic drugs: a strategy of polypharmacy

The amphetamine, an indirect DA receptor agonist, and PCP models of schizophrenia have been developed based on different sets of clinical and preclinical observations. The amphetamine model derives primarily from clinical observations of acute psychotic symptoms and characteristic animal behaviors induced by DA agonists and attenuated by antipsychotic drugs [16]. This model is known to be more relevant to the positive symptoms of schizophrenia. The PCP model has been developed based on observations that NMDAR antagonists induce a broad range of schizophrenic symptoms and unique animal behaviors [55]. PCP-induced animal behaviors are not modified by antipsychotic drugs, but also occur in a sustained hyperdopaminergic state and in monoamine depleted animals [11, 83]. Thus, the amphetamine and PCP models of schizophrenia are associated with their distinctive clinical and preclinical observations and treatment responses. In line with the differential effects of amphetamine and NMDAR antagonists, antipsychotic drugs and glycine site potentiators also differ regarding the target symptoms of schizophrenia. Antipsychotic drugs treat primarily the positive symptoms. They are not likely to treat negative and cognitive symptoms effectively. On the other hand, glycine site potentiators have been shown to improve negative symptoms without affecting positive symptoms significantly, as well as improving some cognitive symptoms. The onset of action of these agents also appears to be different. Antipsychotic drugs are known to take 3–4 weeks to show clear antipsychotic effects. In contrast, glycine site potentiators appear to show therapeutic effects in a progressive manner without a significant latent period [31] (Table 3). Finally, the therapeutic effects of antipsychotic drugs and glycine agonists are different when added to clozapine. In contrast to antipsychotic drugs, glycine agonists can worsen schizophrenic symptoms or fail to improve these symptoms if added to clozapine [26, 33, 117]. We propose a polypharmacy of glycine site potentiators augmented to antipsychotic drugs as a novel therapeutic strategy for the long-term treatment of schizophrenia. Glycine site potentiators and antipsychotic drugs target different symptom clusters through different mechanisms of action and treat the different aspects of the pathophysiology of schizophrenia. Thus, it is quite possible that the augmentation of glycine agonists to antipsychotic drugs could have complementary effects on the long-term treatment of schizophrenic process and attenuate deterioration in schizophrenia.

Conclusion and future direction

This article discussed several important findings regarding the efficacy of glycine site potentiators for schizophrenia as follows: (1) Full glycine agonists, glycine, D-serine and D-alanine and glycine transporter-1 inhibitor, sarcosine, added to antipsychotic drugs improve negative symptoms; (2) It is not clear whether D-cycloserine, a partial glycine agonist, added to antipsychotic drugs, has efficacy in the treatment of schizophrenia; (3) Glycine site potentiators are likely to improve some cognitive symptoms; (4) In contrast to the therapeutic effects of glycine site potentiators added to antipsychotic drugs, glycine site potentiators

added to clozapine do not improve schizophrenic symptoms; (5) Glycine site potentiators combined with antipsychotic drugs may deter the clinical deterioration of schizophrenia; (6) The efficacy of glycine site potentiators on negative symptoms is of particular interest because it may suggest the possibility that drugs potentiating NMDAR function can intervene in the clinical deterioration of schizophrenia. Since the NMDAR complex consists of multiple sites modulating the receptor function such as sites for polyamine and zinc and sites modulating the influx of Ca^{++} through ion channels such as binding sites for Mg^{++} [81] and phencyclidine [86, 121], it is possible that the manipulation of other modulating sites of the NMDAR could also be associated with novel therapeutic strategies in the treatment of schizophrenia.

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