Glycine Transport Inhibitors in the Treatment of Schizophrenia

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Contents

Abstract Schizophrenia is a severe neuropsychiatric disorder without adequate current treatment. Recent theories of schizophrenia focus on disturbances of glutamatergic neurotransmission particularly at *N*-methyl-D-aspartate (NMDA)-type glutamate receptors. NMDA receptors are regulated in vivo by the amino acids glycine and D-serine. Glycine levels, in turn, are regulated by glycine type I (GlyT1) transporters, which serve to maintain low subsaturating glycine levels in the vicinity of the NMDA receptor. A proposed approach to treatment of schizophrenia, therefore, is inhibition of GlyT1-mediated transport. Over the past decade, several well tolerated, high affinity GlyT1 inhibitors have been developed and shown to potentiate NMDA receptor-mediated neurotransmission in animal models relevant to schizophrenia. In addition, clinical trials have been conducted with sarcosine (*N*-methylglycine), a naturally occurring GlyT1 inhibitor, and with

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M.A. Geyer and G. Gross (eds.), *Novel Antischizophrenia Treatments*, Handbook of Experimental Pharmacology 213,
DOI 10.1007/978-3-642-25758-2_12,

the high affinity compound RG1678. Although definitive trials remain ongoing, encouraging results to date have been reported.

Keywords Schizophrenia • *N*-methyl-D-aspartate • Glutamate • Glycine transporter • Negative symptoms • Cognitive dysfunction

1 Introduction

The antipsychotic effect of chlorpromazine and related compounds were discovered fortuitously in the late 1950s, and were subsequently shown to reflect their antagonist potency at D_2-type dopamine receptors (Seeman and Lee 1975). This seminal observation formed the basis for the dopamine theory of schizophrenia—i.e., that symptoms of schizophrenia result primarily from hyperactivity of brain dopaminergic systems. Sixty years later, D_2 antagonists remain the sole approved class of compound for treatment of schizophrenia.

However, the 1950s also provided a second fortuitous discovery, the observation of the psychotomimetic effect of the drug phencyclidine (PCP) (Luby et al. 1959). PCP psychosis, in turn, forms the basis for an alternative theory of schizophrenia that is only now leading to novel therapeutic approaches. PCP induces its unique psychotomimetic effects by binding to an endogenous brain binding site (PCP receptor) that represent a site located within the ion channel formed by the *N*-methyl-D-aspartate (NMDA)-type glutamate receptor (Fig. 1). The ability of NMDA receptor antagonists to induce schizophrenia-like symptoms in normal volunteers leads to the suggestion that endogenous dysfunction or dysregulation of NMDA receptors may be etiological in schizophrenia, and that compounds which stimulate NMDA receptors may therefore be therapeutically beneficial (Javitt and Zukin 1991).

NMDA receptors are modulated by the endogenous amino acids glycine and D-serine, which bind to an allosteric modulatory site of the NMDA receptor (Javitt and Zukin 1989; Johnson and Ascher 1987; McBain et al. 1989) and by glutathione, which binds to a redox site (Sucher and Lipton 1991). Additional modulators include Zn^{2+} and polyamines. These sites provide potential targets for therapeutic development, and encouraging clinical results have been obtained in glycine, D-serine, and glutathione supplementation studies. Nevertheless, the modulatory sites associated with the NMDA receptor to date have proven to be "undruggable" due to their small molecular target, so alternative approaches to modulation of NMDA receptor function have to be developed.

One of the most advanced approaches, at present, is targeting of brain glycine type I (GlyT1) transporters, which are known to regulate brain glycine levels. Since this approach was first proposed in the mid-1990s, numerous high affinity glycine transport inhibitors have been developed by the pharmaceutical industry, and have been shown to induce significant pro-therapeutic effects across a variety of preclinical proof-of-concept assay systems. Most recently, these compounds have

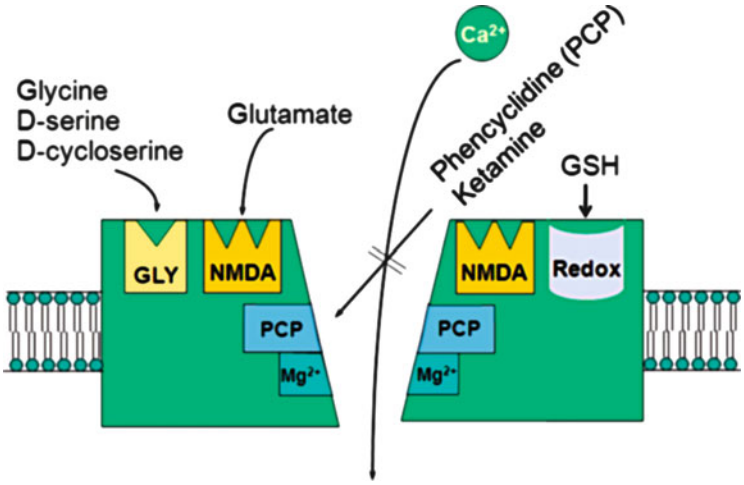

Fig. 1 Schematic model of the *N*-methyl-D-aspartate (NMDA) receptor complex, showing NMDA recognition site and binding sites for glycine (Gly), glutathione (GSH), and phencyclidine (PCP)

completed phase II clinical studies and been entered into definitive phase III clinical trials. Primary targets of studies to date have been persistent negative symptoms, although alternate targets such as prevention, cognitive enhancement, and monotherapy stabilization need to be explored.

1.1 Molecular Structure of NMDA Receptors and Mechanisms of Glycine/D-Serine Modulation

One of the limiting aspects of targeting NMDA receptors is the complexity of NMDA receptor structure. NMDA receptors consist of multiple subunits including at least one NR1 subunit and one or more modulatory subunits from the NR2 (NR2A–NR2D) and/or NR3 (NR3A, NR3B) families. Further eight splice variants have been identified for the NR1 subunits. Each functional NMDA receptor is a heteromultimer, consisting of combinations of NR1, NR2, and/or NR3 subunits.

The different subunits and splice variants significantly alter the functional properties of native NMDA receptors, including their voltage sensitivity, peak conductance, and the degree to which they are influenced by the endogenous modulators such as glycine and D-serine. The glutamate-binding site is located primarily on the NR2 subunits so that NMDA receptors vary in affinity for glutamate based upon subunit composition. In contrast, glycine binds primarily to NR1, although NR2 subunits may nonetheless modulate glycine affinity. Subunit composition also affects sensitivity to other agents. For example, NR2B-containing receptors are sensitive to the polyamine-site ligand ifenprodil (Lynch and Guttmann 2001),

while NR2A containing receptors are highly susceptible to inhibition by Zn^{2+} (Lynch and Guttmann 2001; Paoletti et al. 2009).

NMDA receptor subunit composition varies over space and time in the CNS. During development, NR2B subunits predominate in forebrain, while both NR2A and NR2B are expressed in mature brain. In sensory systems, the switch from NR2B to NR2A is related to sensory experience and coincides with the timing of the critical period for sensory plasticity (Yashiro and Philpot 2008). Conversely, light deprivation increases the ratio of NR2A to NR2B, which lowers the threshold for long-term depression (LTD) and potentiation (LTP) in cortex, increasing metaplasticity of the system (Philpot et al. 2007).

NR2C is found predominantly in developing forebrain (Pollard et al. 1993) and in adult cerebellum, and may be responsible for differential properties of cerebellar versus cortical NMDA receptors (Farrant et al. 1994). NR2D levels are typically low in adults, although upregulation has been reported in prefrontal cortex in schizophrenia (Akbarian et al. 1996). In contrast, a more recent study found selective downregulation of NR1, NR2A, and NR2C subunits in frontal cortex, and no change in NR2B or NR2D (Beneyto and Meador-Woodruff 2008), indicating the need for further investigation.

NMDA receptors are activated by glutamate which is phasically released and reabsorbed, followed by presynaptic activation, and modulated by (1) the amino acids glycine and D-serine, which are tonically modulated by glial interactions and (2) glutathione, which binds to a redox sensitive site. Because of the information contained within temporal coding of glutamatergic pulses, attempts to tonically activate the site with glutamatergic compounds reduces signal-to-noise. Interestingly, while glycine and D-serine have similar, excitatory effects on NMDA receptors containing NR2 subunits, they have opposite effects on receptors containing NR3 subunits, with glycine serving to activate NR3-containing receptors, and D-serine to inhibit them (Chatterton et al. 2002; Madry et al. 2008). Given the complexity of native NMDA receptor structure in brain, relatively little is known about the degree to which they are engaged by specific therapeutic interventions.

1.2 NMDA Receptor Antagonists as Psychopharmacological Models of Schizophrenia

Development of NMDA receptor agents as pharmacological treatments for schizophrenia is based on PCP/NMDA models of the disorder. PCP was first developed in the late 1950s as a potential anesthetic agent, along with the closely related compound ketamine (CI-581) (Chen and Weston 1960; Domino et al. 1965). In preclinical testing, these compounds were found to produce a unique behavioral state in which animals were awake but seemingly "dissociated" from the environment. At higher doses, symptoms such as catatonia were observed in primates that

were highly reminiscent of schizophrenia symptoms (Chen and Weston 1960; Domino and Luby 1981; Javitt and Zukin 1991).

In initial human testing, PCP and ketamine induced an abnormal mental state associated with psychosis. To investigators at the time, this state closely resembled the mental state associated with schizophrenia leading to a series of controlled investigations to examine the similarity and differences between PCP-induced psychosis and schizophrenia, using low, subanesthetic doses of PCP (review in Domino and Luby 1981). These effects were subsequently investigated further using challenge studies with subanesthetic doses of ketamine, in a range of models considered relevant to schizophrenia.

For example, during ketamine administration healthy volunteers show schizophrenia-like deficits in initiation (learning) but not retention of long-term memory similar to those observed in schizophrenia (Hartvig et al. 1995; Krystal et al. 2005; Miyamoto 2006; Morgan et al. 2003; Newcomer et al. 1999; Parwani et al. 2005; Radant et al. 1998; Rowland et al. 2005). Similarly, ketamine induces schizophrenia-like deficits in executive functioning (Krystal et al. 1994, 1998, 1999, 2000), attention/vigilance (Krystal et al. 2005; Malhotra et al. 1996; Oranje et al. 2000; Passie et al. 2005), verbal fluency (Adler et al. 1998; Krystal et al. 1994; Radant et al. 1998), and visual and verbal working memory (Adler et al. 1998; Ahn et al. 2003; Anand et al. 2000; Hetem et al. 2000; Honey et al. 2003; Krystal et al. 1998, 1999, 2005; Malhotra et al. 1996; Morgan et al. 2003; Newcomer et al. 1999). Moreover, in monkeys treated with ketamine (Stoet and Snyder 2006), characteristic schizophrenia-like deficits are reproduced in a task-switching paradigm (Kieffaber et al. 2006; Wylie et al. 2010).

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 (Adler et al. 1999). As opposed to ketamine, amphetamine does not induce neurocognitive deficits of schizophrenia during acute challenge (Krystal et al. 2005).

Sensory dysfunction. Cognitive dysfunction in schizophrenia has, over recent years, shown to extend to sensory-level dysfunction as well. In the auditory system, patients with schizophrenia show deficits in generation of mismatch negativity (MMN), an event-related potential that reflects dysfunction at the level of primary auditory cortex (Javitt et al. 1995; Shelley et al. 1991; Umbricht and Krljes 2005). Similar deficits are observed following intracortical administration of NMDA receptor antagonists in monkeys (Javitt et al. 1996; Javitt 2000), in rodents models (Ehrlichman et al. 2008; Tikhonravov et al. 2008), and during systemic ketamine administration in normal volunteers (Gunduz-Bruce et al. 2012; Heekeren et al. 2008; Kreitschmann-Andermahr et al. 2001; Schmidt et al. 2011; Umbricht et al. 2000) and rodents. Similarly, ketamine induces impairments in proprioception and weight discrimination (Morgenstern et al. 1962; Oye et al. 1992; Rosenbaum et al. 1959) similar to those observed in schizophrenia (Javitt et al. 1999b; Ritzler 1977).

In the visual system, patients show a characteristic pattern of neurophysiological impairment characterized by decreased gain of visual responses within the

magnocellular visual system (Butler et al. 2005). A similar pattern of result is seen following microinfusion of an NMDA receptor antagonist into cat lateral geniculate nucleus (Fox et al. 1990; Kwon et al. 1991). Similarly, patients show deficits in motion detection that reflect impaired motion processing within the magnocellular visual system (Chen et al. 1999; Kim et al. 2005). NMDA receptors play a critical role in the neurophysiological processes underlying motion detection at the neuronal level (Heggelund and Hartveit 1990; Rivadulla et al. 2001) Ketamine challenge studies also show disrupted visual activation during facial gender (Abel et al. 2003b) and emotion recognition tasks (Abel et al. 2003a), suggesting contributions of low level visual deficits to higher cognitive function.

NMDA receptor antagonists reliably induce deficits in sensory gating measures, such as prepulse inhibition (PPI) that closely model the deficits seen in schizophrenia in both rodent (de Bruin et al. 1999; Geyer et al. 2001) and primate (Linn et al. 2003) models. In contrast, ketamine appears to have little effect on either PPI or P50 gating in normal human volunteers (Abel et al. 2003a). The basis for the dissociation between animal and human studies is unknown. However, these findings suggest that gating deficits in schizophrenia may reflect primarily non-glutamatergic pathology.

Although de novo auditory hallucinations are not seen acutely in normal individuals during ketamine intoxication, exacerbation of symptoms is seen in schizophrenia patients during ketamine challenge studies and symptoms observed during the challenge study resemble the patients' acute presenting symptoms (Lahti et al. 2001; Malhotra et al. 1997). In primates, apparent hallucinatory behavior (i.e., threatening nonexistent objects) is not observed during acute PCP treatment, but does emerge during chronic administration (Linn et al. 1999). In a study that applied both amphetamine and ketamine challenge, additive effects were seen only in the case of hallucinations, suggesting that the circuitry underlying hallucinations may have unique sensitivity to both glutamatergic and dopaminergic dysfunction (Krystal et al. 2005).

1.3 Glycine Site Agonists in Treatment of Schizophrenia

Given the ability of NMDA receptor antagonists to induce schizophrenia-like symptoms and cognitive deficits by blocking NMDA receptors, one of the most straightforward predictions of the NMDA theory of schizophrenia is that agents that stimulate NMDA receptor function should be therapeutically beneficial. Furthermore, the glycine/D-serine modulatory site of the NMDA receptor represents an attractive site for intervention since (as opposed to the glutamate site) it is tonically occupied under physiological conditions, and so can be modified using tonic modulation approaches.

Conceptually, for many patients, GlyT1 inhibition will increase glycine/D-serine site occupancy to supranormal levels in order to compensate for overall deficits in NMDA receptor function. However, for some subjects levels of glycine and

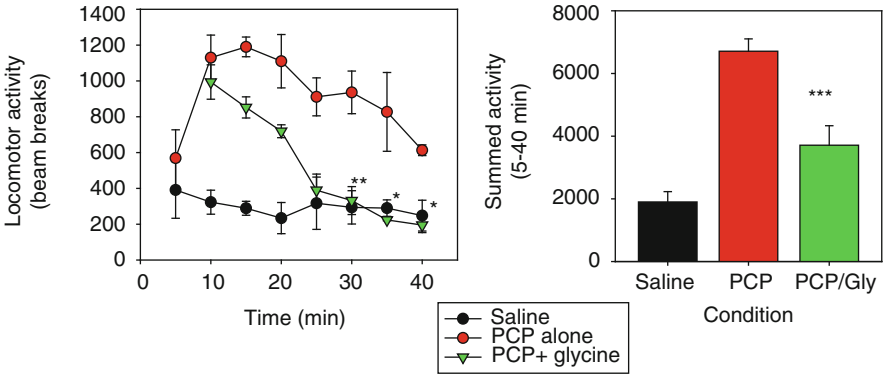

Fig. 2 Earliest findings showing effects of glycine on phencyclidine (PCP)-induced hyperactivity in rodents. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ [from (Toth and Lajtha 1986)]

D-serine have been shown to be reduced in both plasma and CSF (Bendikov et al. 2007; Hashimoto et al. 2003; Neeman et al. 2005; Sumiyoshi et al. 2004), and reduced plasma levels in schizophrenia correlate with severity of negative symptoms (Neeman et al. 2005; Sumiyoshi et al. 2004). Reduced activity of serine racemase (Bendikov et al. 2007), the key synthetic enzyme for D-serine, and increased activity of D-amino acid oxidase (Madeira et al. 2008), the key degratory enzyme, have also been reported. Genetic studies have shown polymorphisms of both serine racemase (Labrie et al. 2009b; Morita et al. 2007) and D-amino acid oxidase/G72 (Corvin et al. 2007; Goldberg et al. 2006; Li and He 2007; Shinkai et al. 2007), suggesting a genetic contribution to disturbances in glycine and/or D-serine synthesis. For subjects with endogenous disturbances in glycine/D-serine metabolism, interventions aimed at increasing brain glycine/D-serine levels may therefore be seen as reversing endogenous dysfunction.

Preclinical studies. The first experimental use of glycine in preclinical models of schizophrenia was performed even before the role of NMDA receptors in mediating effects of PCP and glycine were first demonstrated. In the early-mid 1980s Toth and Lajtha (1981) demonstrated first that large doses of nonessential amino acids do cross the blood–brain barrier when given at large doses, and second that, of a series of amino acids, only glycine reversed behavioral effects of PCP (Toth and Lajtha 1986) (Fig. 2). Similar preclinical effects to those observed with glycine were also observed with D-serine (Contreras 1990).

Subsequently, effects of glycine and D-serine have been confirmed in multiple additional preclinical models relevant to schizophrenia including amphetamine-induced dopamine release (Javitt et al. 2004), latent inhibition (Lipina et al. 2005), and object recognition (Karasawa et al. 2008). These compounds also reverse other cognitive deficits induced by PCP (Hashimoto et al. 2008), reverse effects of perinatal PCP treatment on spatial working memory (Andersen and Pouzet 2004), and enhance social behaviors (Shimazaki et al. 2010). In preclinical models,

relatively high doses of D-serine are required (>600 mg/kg), suggesting the presence of active degratory and sequestration systems that limit D-serine effects.

Clinical studies with glycine. As with preclinical studies, the first clinical study performed with glycine (Waziri 1988)—an open-label study of 25 individuals—was performed before the role of glycine in NMDA receptors was known. Nevertheless, both early experiments provided retrospective support for NMDA receptor-based treatment and prompted subsequent controlled investigation.

The first randomized, double-blind clinical study to show unequivocal significant results was published in 1994 (Javitt et al. 1994b) and showed significant, 17 % reduction in negative symptoms in response to 30 g/day glycine. Subsequent trials of higher dose, 60 g/day glycine also demonstrated significant improvements. In some studies, the degree of negative symptom improvement has correlated significantly with baseline glycine levels, suggesting that patients with lowest pretreatment levels respond best to NMDA receptor agonist treatment (Heresco-Levy et al. 1999).

With glycine, the critical plasma level for therapeutic response was in the range of 600–1,000 μM versus a basal level of approximately 200 μM. Similar levels were also observed in rodent studies, validating the preclinical assay systems (Javitt et al. 2004). To date, only a single multicenter study with glycine has been conducted (Buchanan et al. 2007b). In that study, no significant beneficial effects were found. However, the study was limited by failure to achieve target levels, as well as high placebo response levels. Nevertheless, the large doses of glycine required for clinical treatment make it impractical for widespread therapeutic use, necessitating alternative approaches.

D-serine. Based on positive clinical results with glycine, a series of studies were initiated with the alternative glycine-site agonist, D-serine. The initial clinical trial involved 29 subjects treated for 6 weeks with either D-serine (30 mg/kg/day) or placebo (Tsai et al. 1998). A highly significant ($p = 0.0004$ vs. placebo), mean 20.6 % reduction in negative symptoms was observed among D-serine patients. Significant improvement was noted in neuropsychological function as well, as reflected in WCST categories completed, and CGI.

These results were subsequently replicated in a double-blind, placebo-controlled crossover study (Heresco-Levy et al. 2005) in which D-serine or placebo was added to atypical antipsychotics (risperidone or olanzapine). Highly significant, large effect size (1.3 sd units) improvements were observed in SANS total score and in the negative factor score of the PANSS. Highly significant effects were observed for the PANSS cognitive and depression factors, and total BPRS score as well.

Similar results were also obtained in a study using D-alanine, a lower affinity agonist at the glycine site, at a dose of 0.1 mg/kg (Lane et al. 2005). In contrast to its effects in chronic schizophrenia, D-serine was found to be relatively ineffective in augmentation of effects of risperidone in acute schizophrenia (Lane et al. 2005). Most recently, a multicenter D-serine trial conducted in Israel showed significant reduction in symptoms at 4 weeks, but not subsequently, although results were limited by the high rate of placebo response (Weiser et al. in press).

At present, ideal doses of D-serine for clinical use are unknown and doses are limited by peripheral side effects (nephrotoxicity) rather than efficacy. A preliminary report from an open-label dose escalation PK/PD study found significantly greater improvement in cognition with higher D-serine doses (60–120 mg/kg) than with 30 mg/kg. At high doses, large (>1.0 sd) pre versus post treatment improvements were observed in MATRICS cognition measures along with significant pre–post improvement in PANSS ratings (Kantrowitz et al. 2008), suggesting the need for further, double-blind study of higher D-serine doses.

1.4 Glycine Transport Inhibitors: The Concept

Given the positive clinical experience with glycine/D-serine on the one hand, but the high doses needed to increase brain glycine levels on the other, second-generation approaches to modulate brain glycine levels are clearly required. One of the most advanced approaches, at present, is targeting the brain mechanisms that normally regulate brain glycine levels. Extracellular glycine levels in brain are in the low micromolar range, whereas the affinity of glycine for the NMDA receptor-associated glycine modulatory site is approximately 100 nM. This finding initially led to the concern that glycine levels in brain would be saturated under physiological conditions (Wood 1995). This apparent contradiction was resolved by the observation that NMDA receptors can be "protected" from extracellular levels of glycine by GlyT1 transporters that may be locally co-expressed (Supplisson and Bergman 1997).

GlyT1 transporters are linked to transport of $2Na^+$ ions, and so may maintain gradients of 10,000:1 (Fig. 3a). Given tissue glycine levels in the low mM range, GlyT1 transporters can maintain local concentrations in the synapse of approximately 100 nM, which is close to the EC50 for the glycine site. Glycine affinity may also vary by receptor composition, with NR2A containing receptors, in general, showing lower affinity than NR2B- or D-containing receptors. Thus, modulating glycine levels may disproportionately affect recruitment of NR2A-containing receptors versus those containing other sites (Fig. 3b). In addition, extrasynaptic NMDA receptors are likely saturated by high extracellular glycine levels, and thus are unlikely to be affected by GlyT1 inhibitors.

As opposed to NMDA receptor-associated glycine receptors, inhibitory strychnine-sensitive glycine receptors have much lower affinity for glycine, so even following GlyT1 transporter inhibition these receptors do not become saturated. Furthermore, they appear to be "protected" by both GlyT2 and GlyT1 transporters, which rapidly reabsorb presynaptically released glycine at inhibitory synapses. GlyT2 transporters are linked to $3Na^+$ ions, rather than 2, and thus can maintain much higher glycine gradients.

In brain, GlyT1 transporters are highly co-localized with NMDA receptors and may be co-precipitated with them, suggesting that they may play a physiological role in NMDA receptor function (Zafra and Gimenez 2008). Compounds that inhibit glycine transport would therefore be expected to augment brain glycine

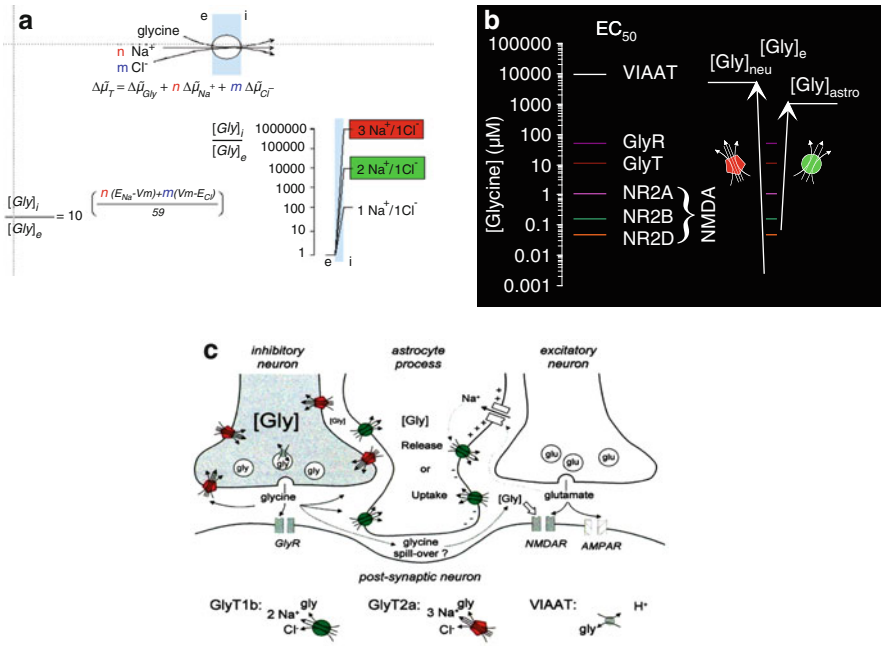

Fig. 3 Schematic illustration of glycine transporter function. (**a**) Glycine type I transporters are coupled to exchange of $2Na^+$ ions, allowing them to maintain an approximately 10,000:1 gradient between intracellular and extracellular space. In contrast, glycine type II transporters, which are linked to $3Na^+$ ions maintain approximately 1,000,000:1 gradients. (**b**) Based on this gradient, the external levels of glycine that can be maintained in the synaptic cleft by GlyT1 transporters on astrocytes is between 0.1 and 1 μM, which is below the level for saturation of NR2B- and NR2A-subunit-containing NMDA receptors. GlyT2 transporters in neurons play a critical role in reabsorbing glycine at synapses containing inhibitory, strychnine-sensitive (GlyR) glycine receptors, and in uptake of glycine into synaptic vesicles in presynaptic terminals in concert with vesicular inhibitory amino acid transporter (VIAAT). (**c**) In the synapse, GlyT1 transporters are co-localized with NMDA receptors, and so maintain subsaturating glycine levels in the synaptic cleft [from (Supplisson and Bergman 1997)]

levels, analogously to the use of selective serotonin reuptake inhibitors (SSRIs) for augmentation of brain serotonin levels. Brain amino acid transporters, in general, are highly selective with well-defined substrate specificity and thus tend to be highly druggable. GlyT1 transporters are encoded by the SLCA9 gene located on chromosome 1p33. Several splice variants are described (Sur and Kinney 2007), but to date have not been shown to have relevance to drug discovery.

Because homozygous GlyT1$^{-/-}$ knockouts are neonatally lethal (Tsai et al. 2004), study of GlyT1 downregulation depends upon either heterozygotes or conditional knockouts. Selective forebrain neuron knockouts show reductions in frontal glycine transport and potentiation of hippocampal NMDA responses as well as pro-cognitive ability on several learning/memory paradigms (Yee et al. 2006). Heterozygous GlyT1$^{+/-}$ knockout mice also show a change in NMDA receptor

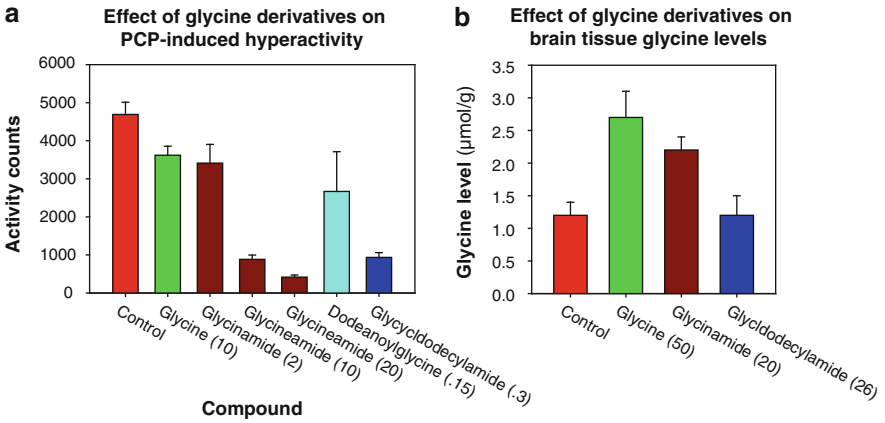

Fig. 4 Initial studies showing effectiveness of glycycldodecylamide (GDA) in animal models of schizophrenia. (**a**) Among glycine derivatives, both glycineamide and GDA were active in reversing PCP-induced hyperactivity. (**b**) As opposed to both gycine and glycineamide, GDA did not increase tissue glycine levels in brain, suggesting that it did not serve as a glycine precursor, raising the possibility of an alternative mechanism of action [from (Toth et al. 1986)]

kinetics, potentially reflecting a net shift from NR2B to NR2A predominance within synaptic versus extrasynaptic NMDA receptors (Imamura et al. 2008).

To date, no evidence of association has been found between GlyT1 polymorphisms and schizophrenia (Deng et al. 2008). Furthermore, GlyT1 expression levels appear unaffected (Burnet et al. 2008), suggesting that GlyT1 inhibitors function by producing compensatory increases in glycine levels to compensate for deficits within other brain systems. Nevertheless, an association has been reported between GlyT1 polymorphisms and methamphetamine-abuse disorder (Morita et al. 2008), and between the gene encoding the GlyT2 transporter (SLCA5) and schizophrenia (Deng et al. 2008), suggesting that GlyT1 inhibitors may ultimately prove useful even in disorders other than schizophrenia.

1.4.1 Glycine Transport Inhibitors: The Early Years

As with glycine, the first studies showing effectiveness of glycine transport inhibitors were performed before their role in modulation of NMDA receptors was known. In the early 1980s, following their studies with glycine, Toth et al. investigated effects of a series of glycine derivatives, including glycineamide, dodecylglycine, and glycyldodecylamide (GDA). Like glycine, several of these derivatives showed significant potency in reversing PCP-induced hyperactivity (Fig. 4a). For most compounds, however, the increases were associated with increases in brain tissue glycine levels (Fig. 4b), suggesting that they served primarily as glycine precursors.

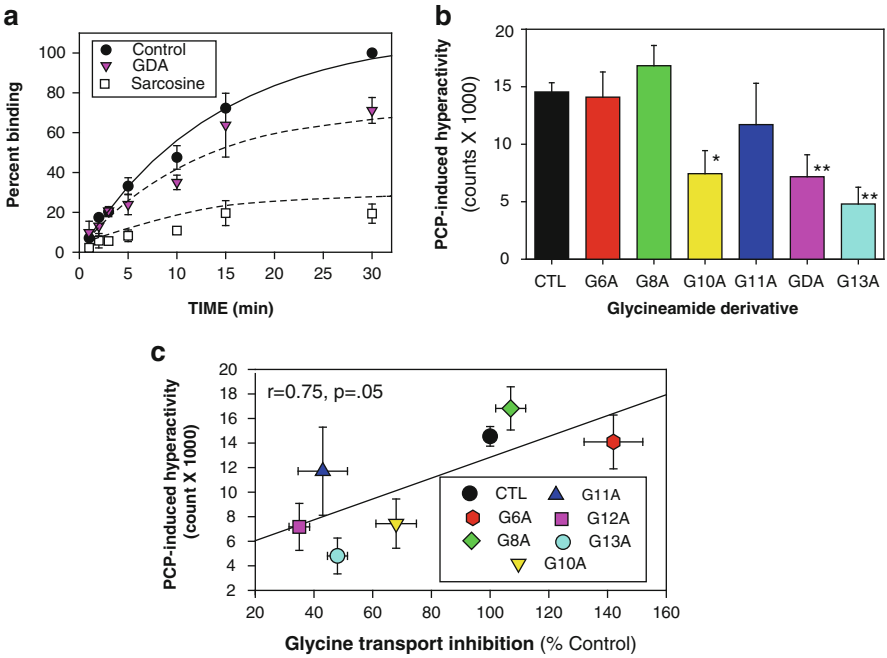

Fig. 5 Initial studies showing effectiveness of GDA and other glycine derivatives in inhibition of glycine transport. (**a**) GDA effects on transport of [^{3}H]glycine in cortical synaptosomal preparation. From (Javitt and Frusciante 1997). (**b**) Relative potency of a range of glycylamide derivatives in reversing PCP-induced hyperactivity in rodents. (**c**) Correlation between efficacy in transport inhibition and efficacy in in vivo efficacy for illustrated glycine transport inhibitors [from (Javitt et al. 1999a)]

GDA, by contrast, had a distinctive effect in which it reversed PCP-induced hyperactivity without raising tissue glycine levels (Toth et al. 1986), raising the possibility that it may be acting by redistributing glycine within brain from the intracellular to the synaptic space, as would be expected from a glycine transport inhibitor. This theory was first tested in the mid-1990s, when it was demonstrated that GDA did, indeed, inhibit glycine transport in cortical synaptosomes (Fig. 5a) (Javitt et al. 1997). Although less potent than the "classic" glycine transport antagonist sarcosine, GDA was nevertheless significantly more potent than other glycine derivatives, suggesting a unique mechanism of action (Fig. 5b). Furthermore, across a range of glycine derivatives, the degree of behavioral inhibition of PCP-induced hyperactivity correlated closely with their potency in inhibiting synaptosomal glycine uptake (Fig. 5c), effects of GDA on synaptosomal glycine uptake, and PCP-induced hyperactivity were subsequently confirmed (Harsing et al. 2001) providing preclinical proof-of-concept for the glycine transport inhibitor approach.

The first high affinity transport inhibitor, N[3-(4′-fluorophenyl)-3-(4′-phenylphenoxy)propyl]sarcosine (NFPS, ALX-5407) (Fig. 6b) was synthesized

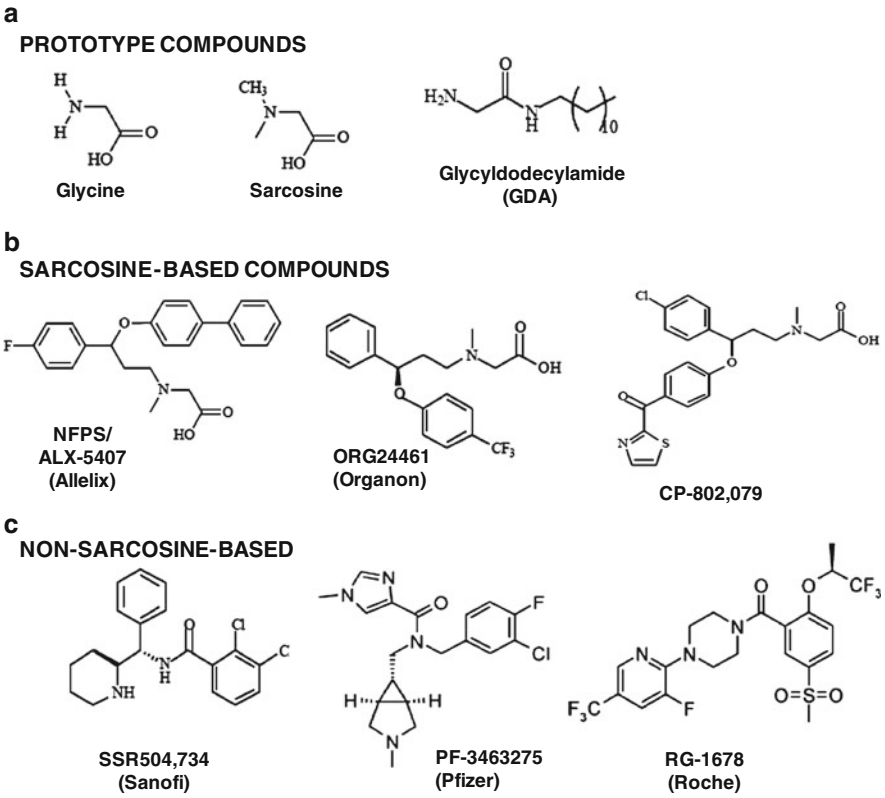

Fig. 6 Structures for prototype compounds (**a**) and representative sarcosine (**b**)- and non-sarcosine (**c**)-based prototype glycine transport inhibitors. For final two compounds, structures have been disclosed but no functional data are available

shortly after completion of the studies with GDA. This compound was derived from the sarcosine backbone with added lipophilic side chains, allowing it to bind but preventing its transport by the GlyT1 transporter (Atkinson et al. 2000, 2001). NFPS, unfortunately, was poorly tolerated in vivo, in part because it produced irreversible GlyT1 inhibition following administration (Aubrey and Vandenberg 2001). Some aspects of toxicity appeared to result from overstimulation of inhibitory glycine receptors in brainstem and cerebellum (Perry et al. 2008b). Nevertheless, NFPS was active and became an early tool compound with studies for investigating consequences of GlyT1 blockade.

Overall, NFPS produced the anticipated effects across a variety of in vitro and in vivo assay systems. Thus, NFPS potentiated NMDA receptor-mediated responses and LTP both in vitro (Bergeron et al. 1998; Chen et al. 2003) and in vivo (Chen et al. 2003; Manahan-Vaughan et al. 2008). In addition, in several assay systems including latent inhibition (Lipina et al. 2005), novel object recognition (Karasawa et al. 2008), social memory (Shimazaki et al. 2010), and other

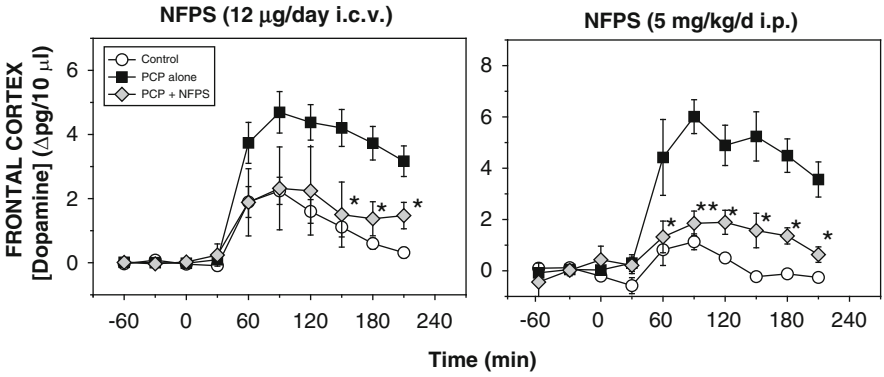

Fig. 7 Effect of a prototype glycine transport inhibitor, NFPS (ALX-5407), on amphetamine-induced dopamine release in frontal cortex, delivered either i.c.v for 14 days (*left*) or i.v. for 3 days (*right*). NFPS significantly inhibited amphetamine-induced dopamine release without altering basal dopamine levels, suggesting potential efficacy against positive, as well as negative, symptoms. $*p < 0.05$, $**p < 0.01$ versus PCP alone [from (Javitt et al. 2005b)]

cognitive models (Hashimoto et al. 2008), NFPS produced effects closely resembling those of D-serine but at substantially lower dose (0.3–1 mg/kg), suggesting that high affinity GlyT1 inhibitors may be clinically viable compounds.

Finally, these compounds significantly reversed PCP-induced alterations in striatal dopamine release both in vivo (Javitt et al. 2004) (Fig. 7) and in vitro (Bennett and Gronier 2005; Javitt et al. 2005b), suggesting that these compounds may be effective against persistent positive, as well as negative symptoms of schizophrenia. Moreover, GlyT1 inhibitors prevent the increase in striatal dopamine release seen following chronic D_2 blockade, suggesting that co-administration of an antipsychotic with a GlyT1 inhibitor may normalize hypofunctional NMDA receptor-mediated glutamatergic neurotransmission with reduced dopaminergic side effects characteristic for antipsychotic medication (Nagy et al. 2010).

In addition to dopamine, GlyT1 inhibitors reverse the inhibitory effect of NMDA/glycine site inhibitors on firing of neurons in dorsal raphe nucleus, suggesting an additional role of NMDA receptors in serotonergic modulation (Papp et al. 2008). As opposed to D_2 blockers, GlyT1 inhibitors do not produce catalepsy in animal models (Harsing et al. 2003), and thus are expected to be free of the type of motor side effects seen with current antipsychotic agents.

1.5 High Affinity GlyT1 Antagonists

Following the success of NFPS in animal models, several, if not most, major pharmaceutical companies initiated screening programs for compounds that would show high affinity and selectivity for the GlyT1 transporter but yet be free of the in vivo toxicity of NFPS. Although some, like NFPS, were derived from a sarcosine background, such as Org 24461 (Brown et al. 2001), CP-802,079

(Martina 2004), Org 24598 (Le Pen 2003), SSR103,800 (Boulay et al. 2008), others were derived from alternative backgrounds derived from high throughput screening (Fig. 6b).

Extensive structure–activity relationships have been published to date by most major pharmaceutical companies including Sanofi (SSR504,734) (Depoortere et al. 2005), Merck (Wolkenberg and Sur 2010), Pfizer (Lowe et al. 2010), Astra-Zeneca (Varnes et al. 2010),Taisho (Terui et al. 2008), and Roche (Pinard et al. 2010b). Structures of these compounds have been extensively reviewed in recent literature (Hashimoto 2011; Wolkenberg et al. 2009; Wolkenberg and Sur 2010). Whether or not GlyT1 inhibitors prove effective in treatment of schizophrenia (or other disorders), the site appears to be highly druggable and argues for the utility of amino acid transporters, in general, as effective targets for drug development.

As opposed to NFPS, most, if not all, of the newer compounds are competitive GlyT1 antagonists with reversible binding kinetics, and thus are better tolerated than earlier noncompetitive agents (Mezler et al. 2008). Structure optimization remains ongoing (Bridges et al. 2008), with focus on improved bioavailability and pharmacokinetics (Wolkenberg et al. 2009). High affinity GlyT1 inhibitors reliably produce increases in CSF and brain dialysate glycine levels (Boulay et al. 2008; Perry et al. 2008a; Yang and Svensson 2008), providing continuing proof-of-mechanism for the GlyT1 approach.

As with glycine and GDA, high affinity GlyT1 inhibitors significantly potentiate hippocampal LTP in vitro (Martina et al. 2004) and inhibit rodent hyperactivity induced by NMDA receptor antagonists such as PCP or MK-801 (Boulay et al. 2008; Singer et al. 2009b; Sur and Kinney 2007; Yang and Svensson 2008), making these among the most reliable high-throughput behavioral screening assays for GlyT1 inhibitor effects. Similarly, newer glycine transport inhibitors, as with GDA and NFPS, also reverse NMDA receptor antagonist induced abnormalities in persistence of latent inhibition (Black et al. 2009), reverse PPI deficits in DBA mice (Boulay et al. 2008; Sur and Kinney 2007), and attenuate acquisition and retention of contextual fear conditioning (Nishikawa et al. 2010). In monkeys, the novel GlyT1 inhibitor PF-3463275 (Fig. 6c) reversed ketamine-induced spatial memory deficits, providing further proof-of concept across species (Roberts et al. 2010).

Although the majority of preclinical studies have investigated reversal of cognition-disrupting effects of noncompetitive NMDA receptor antagonists, it has recently been suggested that glycine site antagonists such as L-687,414 may induce rodent hyperactivity that is highly sensitive to effects of GlyT1 inhibitors (Alberati et al. 2010). This model therefore may be more particularly sensitive as a screening tool for agents acting at the glycine-binding site of the NMDA receptor.

Extracellular glycine. Extracellular glycine levels observed following GlyT1 inhibitor treatment are dramatically lower than those observed during treatment with behaviorally effective doses of glycine. These findings are consistent with a model in which GlyT1 inhibitors primarily affect glycine concentrations within

the synaptic cleft, which represents a separate brain compartment from the overall extracellular space. Whereas CNS levels in glycine-treated animals reflect those necessary to insure glycine diffusion into the synaptic space from the extracellular space, extracellular levels in GlyT1 inhibitor-treated animals most likely reflect back-diffusion from the synaptic to the extracellular compartment. Thus, effective stimulation of synaptic NMDA receptors occurs at doses that do not necessarily increase overall extracellular glycine levels and relatively modest increases in extracellular glycine may reflect substantial increases in the much-smaller synaptic space.

In order to support clinical development programs, most companies, at present, require PET ligands or other proof-of-mechanism biomarkers. Several compounds have been identified to date that may serve as clinically effective PET ligands to guide future drug development (Hamill et al. 2011; Herdon et al. 2010; Zeng et al. 2008). At high doses, stimulatory effects of glycine and GlyT1 inhibitors (sarcosine, CP-802,079) may be lost due to presumed NMDA receptor internalization (Martina 2004), raising concern about potential inverted U-shaped dose response curves in clinical studies. Thus, optimal doses of GlyT1 inhibitors may be below those necessary to significantly elevate CSF or microdialysate glycine levels, or to fully occupy the GlyT1 transporter site. Potential for internalization also argues for consideration of intermittent, rather than persistent, dosing strategies. Even at high doses, GlyT1 inhibitors seem to have limited toxicity. Thus, it is possible that negative clinical data will be obtained based upon clinical doses that are too high, as well as too low, in total occupancy of the GlyT1 site.

1.5.1 Clinical Studies with Glycine Transport Inhibitors

Clinical support for the GlyT1 approach comes both from studies of sarcosine (*N*-methylglycine) conducted in Taiwan, and from initial results of a phase II study conducted using the high affinity GlyT1 inhibitor [4-(3-fluoro-5-trifluoromethylpyridin-2-yl)piperazin-1-yl][5-methanesulfonyl-2-((*S*)-2,2,2-trifluoro-1-methylethoxy)phenyl]methanone (RG1678, Roche) (Pinard et al. 2010a).

Sarcosine. Sarcosine is a naturally occurring metabolic intermediate of glycine metabolism that cross-reacts with GlyT1 transporters with low (~13 μM) affinity (Yang and Svensson 2008). Safety of sarcosine treatment is supported by clinical experience with sarcosinemia, an inborn error of metabolism in which extremely high peripheral sarcosine levels are observed without apparent toxic effect. Nevertheless, high sarcosine levels were linked to increased invasiveness of prostate cancer in one study (Sreekumar et al. 2009), although this finding has not been confirmed (Struys et al. 2010). In addition, sarcosine, at present, is not available in an FDA-approved formulation. Thus, clinical studies with sarcosine remain limited.

Initial studies with sarcosine showed efficacy similar to that of direct glycine-site agonists (i.e., glycine, D-serine, and D-alanine) when added on to either typical or non-clozapine atypicals in chronic stabilized inpatients (Lane et al. 2005). Sarcosine was also found to be relatively ineffective in combination with clozapine, consistent with prior studies that used direct glycine-site agonists (Lane et al. 2006).

In all these studies, medications were used at single, non-optimized doses, raising the possibility that greater efficacy and different comparative effects might be observed at higher doses.

Most recently, sarcosine was also associated with significant reduction in symptoms in a small monotherapy trial in acutely decompensated subjects, although the absence of a placebo arm complicates interpretation of the study (Lane et al. 2008). Despite the small sample size and limited design, the monotherapy study represents a critical evolution of the NMDA receptor-based therapeutic approach, and argues for monotherapy, as well as adjunctive treatment, trials for high affinity GlyT1 inhibitors.

RG1678. To date, several high-affinity GyT1 inhibitors have been entered into clinical studies, suggesting successful preclinical development and relatively absence of toxicity in phase I clinical trials. In addition, several small scale studies with high affinity GlyT1 antagonists are listed as ongoing or complete (http://www.clinicaltrials.gov), although results from most of these remain lacking. The only study to have reported out findings to date was a phase II study with the novel compound RG1678. Thus far, results have been made available only in abstract form based upon meeting presentation (Umbricht et al. 2010), and thus are not yet peer reviewed. Nevertheless, reported clinical results are encouraging and have led to initiation of a phase III clinical development program for this compound.

2 Unresolved Issues in NMDA Receptor-Based Treatment Development

The recent reported positive phase II results with RG1678, coupled with earlier reports of successful clinical trials with sarcosine, suggest that the GlyT1 approach may lead to significant modulation of NMDA receptor-mediated neurotransmission in vivo. As with all novel classes of compound, however, ideal uses of these compounds will require clinical experimentation and clinical effectiveness may not be predictable based upon preclinical models. In schizophrenia, critical issues such as optimal patient populations and ideal biomarkers for evaluation of treatment response still need to be determined, as well as potential side effects that might be observed during chronic treatment. Potential synergistic effects among different mechanisms should also be considered. Given the general involvement of NMDA receptors in learning, memory, and cortical plasticity, the possibility that NMDA receptor manipulation might be effective in other conditions should also be evaluated.

Optimal patient population. At present, ideal patient populations and target symptoms for NMDA receptor-based treatment remain unknown. Although NMDA theories are most associated with negative and cognitive symptoms, in fact, increases in positive symptoms are observed as well following PCP/ketamine challenge, and improvement in total symptoms are typically as large or larger than improvements in negative symptoms in most NMDA receptor-based treatment

studies (Javitt 2006). Evidence for effects of NMDA receptor-based treatments on cognition have been limited thus far, but this may be a function of the limited range of dosing that is possible with available agents.

Based upon NMDA theories, GlyT1 inhibitors would be expected to be most effective in individuals showing symptoms corresponding most closely to the expected NMDA phenotype. In general, such individuals might best be characterized by the following features: poor premorbid function, slow and incomplete response to antipsychotic agents, and relatively generalized nature of neurocognitive dysfunction. In such individuals, total symptoms would probably improve most in response to NMDA receptor-based treatments. Although NMDA receptor-based treatments should also produce beneficial effects on cognition, treatments may need to be paired with ongoing neurocognitive remediation in order to produce robust behavioral improvement.

In studies performed to date, the best response to NMDA receptor modulators has been observed in individuals receiving lowest doses of antipsychotic medication (Javitt 2006). Because clozapine at high dose may interfere with amino acid transport via the System A transport system (Javitt et al. 2005a), inclusion of clozapine-treated individuals should probably be avoided.

Encouraging preliminary results have been obtained over recent years in the treatment of individuals showing prodromal symptoms of schizophrenia (Woods et al. 2004). To the extent that NMDA receptor-based treatments can restore normal brain plasticity, ideal use of these compounds may be in prodromal stages of the disorder with the goal of preventing progression to psychosis and thus modifying the course of the illness rather than simply controlling ongoing symptoms.

Peripheral toxicity. In brain, GlyT1 transporters appear linked primarily to NMDA receptors, so limited off-site toxicity is observed. However, GlyT1 transporters are also present in immature erythrocytes (Weigensberg and Blostein 1985) and in retina, producing potential for side effect. The role played by GlyT1 in erythrocyte maturation and heme synthesis is not well established, but could potentially lead to hematological side-effects such as anemia during clinical treatment. Conversely, GlyT1 mediated transport functions appear to be lost during erythrocyte maturation so hematological effects may be limited (Felipe et al. 1990).

In retina GlyT1-mediated transport appears to be the primary source of glycine rather than de novo synthesis. For example, treatment with sarcosine was found in one study to deplete glycine levels (Pow 1998). Furthermore, exposure to serine did not rescue cells from consequences of glycine transport inhibition, suggesting relatively limited de novo synthesis (Pow 1998). In addition, GlyT1 may play a key role in regulation of NMDA in retina (Marc 1999), as in brain, but may be more susceptible to blockade because of retina's location outside of the blood–brain barrier. NMDA receptors in retina are reported to participate to a greater degree in ON- versus OFF-pathway responses (Kalbaugh et al. 2009). In contrast, visual deficits in schizophrenia are observed in OFF- as well as ON-pathways, suggesting that these are more likely to result from NMDA receptor dysfunction at post-retinal stages of visual processing (Butler et al. 2008).

Combination with glycine. The large majority of preclinical studies with prototype compounds have been conducted using monotherapy. However, the combination of glycine and GlyT1 inhibitors has been observed to produce multiplicative effects on extracellular brain glycine levels (Yang and Svensson 2008). Whether this interaction will enhance behavioral activity of GlyT1 inhibitors or will simply increase side effects and/or prompt internalization of NMDA receptors remains unknown, but should be explored at least in preclinical models.

An additional potential use of combined glycine and GlyT1 inhibitor treatment is the management of peripheral side-effects. Glycine treatment in schizophrenia is limited by poor CNS penetration. Nevertheless, high peripheral glycine concentrations can easily be achieved through dietary supplementation. Peripheral side effects with GlyT1 inhibitors will be most severe with compounds that have poor CNS penetrance. However, for competitive compounds, peripheral side effects can easily be overcome by glycine supplementation.

Finally, a concern with use of GlyT1 inhibitors is that, over time, they may lead to depletion in whole brain glycine concentration, due to outward diffusion of glycine from the extracellular compartment. Since brain glycine is synthesized de novo from serine rather than being derived from the periphery, glycine metabolism would have to increase to compensate for the increased efflux. Whether or not this occurs has not been determined. As with peripheral side effects, such depletion could likely be overcome even by modest supplementation with dietary glycine.

Combination treatments. Because both glycine and D-serine modulate NMDA receptors in parallel, little is known about what, if any, compensations may result from sustained GlyT1 inhibitor-induced elevations in synaptic glycine levels. Combined GlyT1 inhibitor and D-serine treatment is feasible but effects of combined treatment have not been evaluated even in animal models. Because the two sets of compounds converge on NMDA receptors but otherwise engage nonoverlapping metabolic pathways and outside targets (Fig. 8), combined treatment may provide greater efficacy and larger safety margins than treatment with either set of compounds alone.

Similarly, NMDA receptors are modulated by glutathione, as well as by glycine/D-serine. As with glycine and D-serine, reductions in glutathione levels have been reported in schizophrenia (Altschule et al. 1959; Do et al. 2000; Yao et al. 2006), related to underlying genetic disturbances (Gravina et al. 2011). Furthermore, treatment with *N*-acetylcysteine (NAC), a glutathione precursor, has been reported to reverse neurophysiological deficits in schizophrenia (Lavoie et al. 2008) and to ameliorate persistent negative symptoms (Berk et al. 2008; Dean et al. 2011).

At present, little is known about the degree to which parallel manipulation of the glycine/D-serine and glutathione sites of the NMDA receptor may lead to supra-additive effects, although older literature suggests potential synergies with decreased risk of desensitization (Benveniste and Mayer 1993; Javitt et al. 1994a). Other potential targets, including α7 nicotinic receptors and mGluR2-type glutamate receptors that regulate presynaptic glutamate release (Buchanan et al. 2007a; Mexal et al. 2005; Moghaddam and Javitt 2012; Toth et al. 1992) and mGluR5-type glutamate receptors that modulate postsynaptic NMDA receptor activation (Javitt et al. 2011; Lindsley et al. 2006) also show promising results in

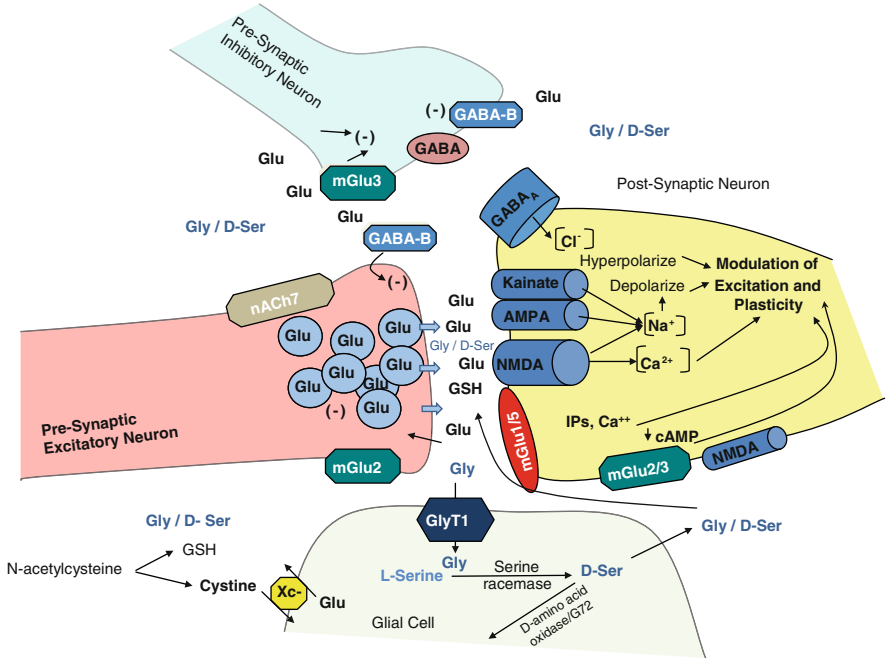

Fig. 8 Schematic diagram showing potential interaction between GlyT1 and other relevant drug development targets including α7 nicotinic (nACh7), GABA-A and B receptors, metabotropic type 2 (mGluR2). 3 (mGluR3) and 5 (mGluR5) receptors, and cystine/glutamate antiporters (xC)

isolation, but may show synergistic effects when combined with a glycine site agonists. As combined treatment studies are difficult to perform in clinic, preclinical studies are needed to identify potentially synergistic pharmacological combinations.

2.1 Other Indications

NMDA receptor-based treatments have been most extensively studies, to date, for management of schizophrenia. However, given the widespread role of NMDA receptors in brain functioning, use of these compounds in a range of other disorders may also be envisioned.

Substance abuse. In the clinical situation, comorbidity of schizophrenia and substance abuse disorders including alcohol abuse is high, suggesting the possibility of shared glutamatergic pathology (Coyle 2006). In rodents, the GlyT1 inhibitor Org 35935 has been found to decrease ethanol intake along with alcohol induced increases in striatal dopamine levels (Lido et al. 2009; Molander et al.

2007). Recently, alcohol-abusing subjects have been observed to have relative insensitivity to cognition-impairing effects of high dose D-cycloserine, and relative insensitivity to glycine/D-cycloserine pharmacodynamic interactions (Krystal et al. 2011). Overall, while supporting theories of glutamatergic disturbance in alcoholism, these findings leave unresolved the degree to which up- or downregulation of glutamatergic function is desired.

Obsessive compulsive disorder. Another potential target for glycine-based treatments is obsessive-compulsive disorder (OCD). OCD may be conceptualized as a failure of "reversal learning" in which pathological associations cannot be unlearned and therefore dominate behavior. Thus, compounds that stimulate NMDA receptor function may assist in unlearning these pathologically learned associations.

An initial study with glycine showed significant benefit (Greenberg et al. 2009). More recently, similar effects have been observed with sarcosine (Wu et al. 2011). Although high affinity GlyT1 inhibitors have not yet been tested in OCD models, it has been demonstrated that deletion of GlyT1 transporters in forebrain significantly potentiates reversal learning (Singer et al. 2009a), suggesting a potential pro-therapeutic effect. Similar effects have been demonstrated following administration of D-serine (Duffy et al. 2008) or upregulation of cortical D-serine levels in cortex by deletion of its degratory enzyme (D-amino acid oxidase) in forebrain (Labrie et al. 2009a), supporting a role for NMDA enhancers in treatment of OCD as well as schizophrenia.

Movement disorders. NMDA receptors are highly expressed in basal ganglia as well as in cortex, and are known to play a prominent role in regulation of subcortical dopamine release (Javitt and Zukin 1991; Javitt et al. 2005b). The prevailing view in most movement disorders research is that excessive NMDA receptor activation may lead to excitotoxicity, and therefore that NMDA receptor antagonists should be therapeutically beneficial (Bagetta et al. 2010; Bonuccelli and Del Dotto 2006). However, clinical trials conducted with NMDA receptor antagonists in Parkinsons disease have not, to date, been successful.

An alternative viewpoint is provided by the observation that in several trials conducted in schizophrenia, significant improvement was observed in antipsychotic-induced Parkinsonian symptoms and tardive dyskinesia during treatment with either glycine (Heresco-Levy et al. 1999; Heresco-Levy and Javitt 2004) or D-serine (Heresco-Levy et al. 2005; Kantrowitz et al. 2010). This finding has subsequently been confirmed in a small-scale clinical study conducted in Parkinson's disease (Gelfin et al. 2012). To the extent that beneficial effects of D-serine can be confirmed in larger studies, future trials with high affinity GlyT1 inhibitors are warranted.

3 Concluding Remarks

The pace of new drug development in neuropsychiatric disorders such as schizophrenia is frustratingly slow. Most medications used presently differ little from those used half a century ago. The theoretical underpinnings for use of GlyT1 inhibitors date back to the original development of PCP models of schizophrenia in the 1960s, and linkage of these models to dysfunction of NMDA receptors in the 1990s. At present, GlyT1 inhibitors are just one of many approaches that are seeking to modulate glutamatergic neurotransmission in general and NMDA receptors in particular for treatment of schizophrenia. Thus far, both preclinical findings and early clinical results with the high affinity compound RG1678 have been encouraging, but failure rates of novel mechanisms, even in phase III clinical trials, remain high.

Over the last 20 years, there has been an explosion of information regarding mechanisms of glutamatergic transmission in brain, but this increased knowledge has not yet led to new approved treatments for neuropsychiatric illness. At present, many glutamatergic compounds are "in play," including mGluR2/3 and mGluR5 agonists for schizophrenia, mGluR5 antagonists for autism, glutamate/cystine antiporter antagonists for substance abuse, and NMDA receptor antagonists for depression (Javitt et al. 2011). Success of any of these mechanisms will help validate the glutamatergic system as an appropriate target for therapeutic intervention, not only for schizophrenia in specific, but also for neuropsychiatric disorders in general, and thus may pave the wave for a new "golden age" of psychopharmacology.

Disclosures Dr. Javitt holds intellectual property rights for use of NMDA receptor agonists, including glycine, D-serine, and glycine transport inhibitors in treatment of schizophrenia. Dr. Javitt is a major shareholder in Glytech, Inc. and Amino Acids Solutions, Inc. Within the past year, Dr. Javitt has served as a paid consultant to Sunovion, Lilly, BMS, and Takeda.

Acknowledgments Support: This work was supported in part by NIH grants R37 MH049334, P50 MH086385, R01 DA03383 and U01 MH074356.

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