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Glycinergic signaling in the human nervous system: An overview of therapeutic drug targets and clinical effects

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Abstract

Glycine and related endogenous compounds (D-serine, D-alanine, sarcosine) serve critical roles in both excitatory and inhibitory neurotransmission and are influenced by a multitude of enzymes and transporters, including glycine transporter 1 and 2 (GlyT1 and GlyT2), D-amino acid oxidase (DAAO), serine racemase (SRR), alanine-serine-cysteine transporter 1 (Asc-1), and kynurenine aminotransferase (KAT). MEDLINE, Web of Science, and PsychINFO were searched for relevant human trials of compounds. Many studies utilizing exogenous administration of small molecule agonists of the glycineB site of N-methyl-D-aspartate receptor have been studied as have a growing number of glycine transporter type 1 (GlyT1) inhibitors. The clinical effects of these compounds are reviewed as are the potential effects of newer novel compounds.

Keywords: glycine, NMDA, D-serine, D-alanine, bitopertin, glycine transporter 1 inhibitors, D-amino acid oxidase, rapastinel, antipsychotic augmentation

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Introduction

The physiological role of glycine as a transmitter in the central nervous system (CNS) is complex, and the understanding of its processing reveals a variety of potential therapeutic targets, many of which have been explored. Classically, glycine is considered an inhibitory neurotransmitter alongside gamma-amino butyric acid (GABA), and glutamate is the primary excitatory neurotransmitter.[1] In the brain stem and spinal cord, glycinergic neurons release glycine to act on strychnine-sensitive glycine receptors (GlyRs, also called the glycine-A binding site), which are ligand-gated ion channels structurally homologous to GABA-A, serotonin type 3 ($5HT_3$), and nicotinic acetylcholine (nAChR) receptors.[1] Glycine also functions as a requisite coagonist on the N-methyl-D-aspartate (NMDA) subtype of ionotropic glutamate receptors and, as such, facilitates excitatory neurotransmission.[2] Although this site is often called the *glycine modulatory site* (GMS) of the NMDA receptor (also delineated as glycineB), the primary endogenous ligand for synaptic NMDA receptors (NMDAR) has been shown to be the racemate D-serine.[3]

In addition to glycine receptors, 2 glycine transporters (GlyT1 and GlyT2) have been cloned and function to remove glycine from the synapse (Figure).[4] GlyT1 is located on the surface of astrocytes in both excitatory and inhibitory synapses as well as on the presynaptic side of excitatory (glutamatergic) synapses. GlyT1 maintains a subsaturating concentration of glycine in the excitatory synapse.[5] In contrast, GlyT2 is located on the presynaptic surface of inhibitory (glycinergic) synapse.[6,7]

Beyond glycine receptors and transporters, enzymes involved in the metabolism of glycine, D-serine, and kynurenic acid (an endogenous antagonist of the glycineB

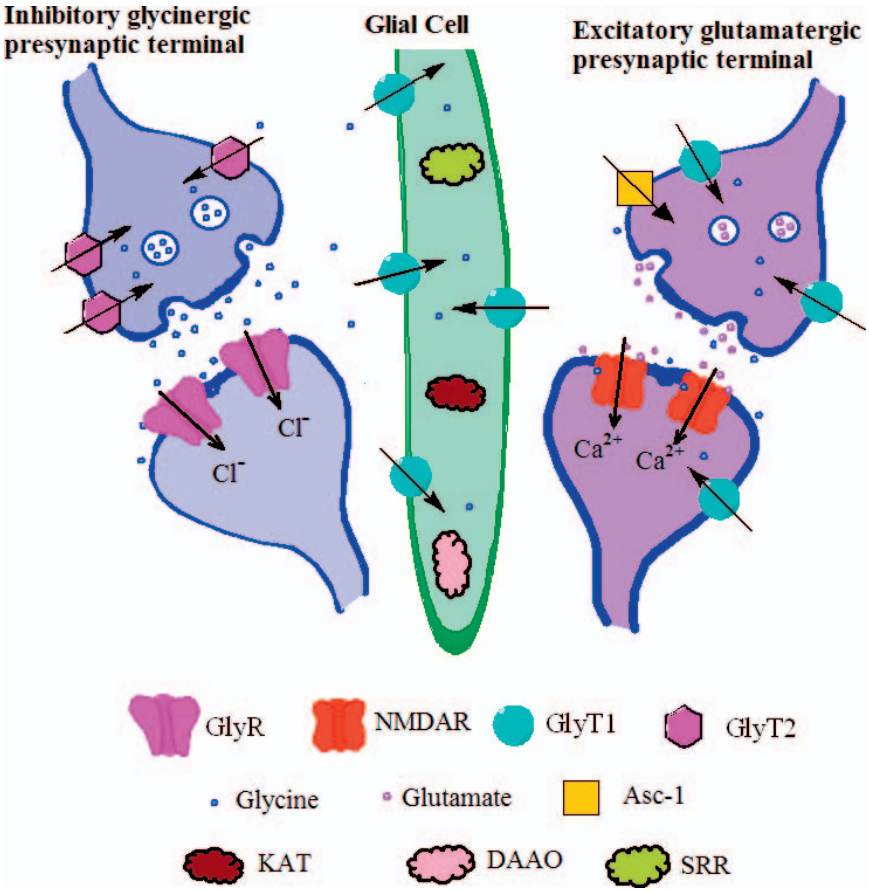

FIGURE: Summary of receptors, enzymes, and transporters for glycine at glycinergic and glutamtergic synapses. At inhibitory glycinergic synapses, both presynaptic glycine transporter 2 (GlyT2) and GlyT1 on glial cell surfaces help to regulate extracellular concentrations of glycine. Excitatory glutamatergic synapses with N-methyl-D-aspartate receptors (NMDAR) require both glutamate binding and binding to the glycineB site, usually by D-serine. Alanine-serine-cysteine transporter 1 (Asc-1) can remove D-serine from the synapse into presynaptic terminal bouton. Kynurenine aminotransferase (KAT), D-amino acid oxidase (DAAO), and serine racemase (SRR) are present in glial cells and are involved with the metabolism of D-serine and other ligands discussed in the text.

site) may also represent potential targets for pharmacotherapy as there is evidence that these systems may be altered in schizophrenia.[8,9] These include D-amino acid oxidase (DAAO), serine racemase (SRR), alanine-serine-cysteine transporter-1 (Asc-1), and kynurinene aminotransferase (KAT).

This review focuses on the knowledge of current therapeutics' impact on glycine-related sites of action, clinical trials of glycine-specific agents (glycine, D-serine, D-alanine, and sarcosine) as both monotherapy and augmentation strategies, and phase 3 trials of agents in development, which are limited primarily to GLYT1 inhibitors. To limit the scope of this review, studies of the glycineB site partial agonist D-cycloserine (DCS) will not be reviewed in depth. Briefly, because the NMDAR plays a key role in long-term potentiation and therefore learning, DCS has been studied to augment a variety of cognitive behavioral therapies and exposure therapies to help reinforce learning during these sessions. The efficacy of this intervention is largely dependent on the effect of the individual session of psychotherapeutic intervention.[10] First, an overview of glycinergic neurotransmission will prepare the reader for discussion of the clinical trial results covered by the literature review.

Biochemistry and Pharmacology of Glycinergic Neurotransmission

Inhibitory signaling via glycine takes place primarily in the spinal cord, brain stem, and caudal brain and requires action at GlyRs on postsynaptic neurons.[11] Both motor and afferent sensory pathways (audition and vision) rely on glycinergic signaling. GlyRs are ligand-gated ion channels, which are primarily permeable to chloride ions. Chloride ion influx leads to hyperpolarization of the post-synaptic cell, which inhibits propagation of an action potential. The glycine receptor has a limited number of known endoge-

nous agonists, which are potent in the order of glycine > β-alanine > taurine > D- or L-alanine > L-serine >> D-serine.[12,13]

GlyRs are antagonized by the alkaloid strychnine with high affinity, and therefore GlyRs are generally referred to as *strychnine-sensitive* to distinguish them from the glycine binding site on the NMDAR, which is sometimes referred to as *strychnine-insensitive*.[14] As mentioned previously, the GlyT2 glycine transporter is localized to these inhibitory synapses, making specific inhibition of these transporters a potential influence on inhibitory glycinergic action.[7]

GlyR and GlyT2 are potential therapeutic targets for a number of conditions. As strychnine is a convulsant, modulating the activity of glycine receptors is an attractive target for the treatment of epilepsy.[13,15] GlyR mutations are implicated in the neurodevelopmental disorder hyperekplexia, also known as startle disease, in which unexpected auditory or visual stimuli trigger an exaggerated startle response accompanied by a brief period of muscular stiffness. Other conditions marked by exaggerated startle (eg, anxiety disorders, post-traumatic stress disorder) may therefore be influenced by modulating this system.[16] The inhibitory role of glycine in spinal cord and brain stem neurotransmission has been exploited in efforts to treat chronic neuropathic pain as well.[17,18] Abnormalities related to the neurodevelopmental role of glycine have been linked to autism and neurodegenerative disease.[16]

The role of glycine and related molecules acting at the glycineB site of the NMDAR has been studied extensively and has far-reaching clinical implications commensurate with the wide distribution of these receptors. The NMDAR serves key functions in cognition, learning, and memory.[19] Binding of a coagonist ligand to the glycineB site is required for the ion channel to open. The concentration of glycine in cerebrospinal fluid is high, but there is evidence that the coagonist site of NMDAR is not generally saturated in vivo due to glycine transport out of the synapse.[5,20] D-serine appears to be the primary coagonist for NMDARs localized to the excitatory synapse and is the predominate coagonist involved in NMDA-elicited neurotoxicity.[21,22] D-serine concentration is regulated primarily by the activity of 3 proteins: SRR, which converts L-serine into D-serine; DAAO, which is responsible for the degradation of D-serine; and Asc-1, which removes D-serine from the synapse (Figure). All 3 proteins are potential targets for therapeutics although only DAAO inhibitors have reached clinical trials.[23,24]

The NMDA-hypofunction hypothesis of schizophrenia is elegant in that antagonists (eg, phencyclidine, ketamine) at this receptor induce both positive and negative symptoms as well as cognitive deficits in healthy humans that mimic those seen in schizophrenia.[25] Glycine and related molecules function as positive allosteric modulators of NMDA activity and so would be expected to improve the symptoms of schizophrenia. Direct overstimulation of NMDARs is excitotoxic and leads to neuronal cell damage and death.[26] Because of this, agents designed to reduce NMDA activity have been explored to minimize the effects of excitotoxic conditions (eg, stroke or head trauma). A more recent line of research has focused on the observed antidepressant effects of the NMDAR antagonist ketamine and subsequent development of similar molecules (reviewed previously by Wijesinghe[27] in this journal). The dependence of NMDA function on glycine makes this site interesting for depression as well. Finally, because of the role of NMDARs in long-term potentiation and learning, glycineB agonists have been studied as cognitive enhancers.

Methods

Online databases MEDLINE, Web of Science, and PsycINFO were searched by lead author (R.S.) with combinations of terms glycine, receptor, transporter, inhibitor, D-serine, D-alanine, sarcosine, serine racemase, D-amino acid oxidase, kynurenic acid, neurotransmission, and psychiatry and limited to human clinical trials in English with no date limitations. Trials of the glycineB partial agonist DCS were not included to limit the scope of the review. Searches were conducted initially in December 2015 and repeated throughout the peer review process, ending in May of 2016. Titles, abstracts, and related articles were examined for relevance to the current topic as were article references when appropriate. Other resources were used to expand background information when necessary and provide some preclinical information when pertinent.

Results

Glycine-B Agonists

As a group, the endogenous glycineB agonists (glycine, D-serine, and D-alanine), when administered exogenously, are less than ideal pharmacologic agents due to poor brain penetrance. Studies also have shown more positive results in the short term and lack of effect in longer, larger trials. This may be related to the observation that activation of the glycineB site primes endocytosis of the NMDAR, leading to NMDAR internalization.[28]

Glycine

Exogenous glycine has been studied in the treatment of a variety of conditions, including schizophrenia and its prodrome, obsessive-compulsive disorder, and pain

syndromes. Taken as a whole, these studies have had somewhat mixed results. This is likely related to individual differences in study design, small samples, and ranges in dose.[29-32] Glycine transport across the blood-brain barrier is low, but CSF levels can be influenced in a dose-dependent manner by moderate-to-high doses.[33]

A 2010 meta-analysis of studies with glycinergic coagonists for the treatment of schizophrenia included an analysis of the dose-response of glycine based on 10 studies for this indication. It has been given in doses ranging from 15 to 60 g/d, most often dosed as 0.8 g/kg of total body weight.[34] The investigators found glycine treatment to be significantly effective on measures of total psychopathology, positive symptoms, and depressive symptoms, but no dose-response relationship was found. Regardless of indication, the large doses of glycine required for positive treatment effects may be poorly tolerated due to gastrointestinal side effects and poor taste.[34,35]

A report[36] of 2 short-term trials of glycine monotherapy for patients identified to be at risk for developing schizophrenia (using the Criteria of Psychosis-risk Syndromes) found positive results on the Scale of Psychosis-risk Symptoms (SOPS) and Montgomery-Asberg Depression Rating Scale (MADRS). These were an open-label trial in 10 patients for 8 weeks, followed by 16 weeks to evaluate for treatment durability and a 12-week placebo-controlled trial in 8 patients (4 per treatment arm). The dose was titrated over the course of 11 days to the target dose of 0.4 mg/kg twice daily, capped at 80 g total daily dose in both studies. These studies incorporated microencapsulated preparations of glycine to improve palatability. The open-label trial had significant improvement in all outcome measures (SOPS-total, positive, negative, disorganized, general, and MADRS). In the placebo-controlled trial, the only statistically significant between-group effect was an improvement on MADRS (effect size -2.06, $P < .05$). These trials are limited by the sample size and the allowance for background pharmacotherapy other than antipsychotics (however, this was limited to just one patient in each treatment arm being treated with an antidepressant in the placebo-controlled trial).

Greenberg et al[35] studied in a randomized placebo-controlled fashion the effect of adjunctive glycine titrated to 30 g twice a day for 12 weeks on obsessive-compulsive disorder severity as assessed by the primary outcome measure, the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). Participants were allowed to continue unchanged psychopharmacological regimens and/or psychotherapeutic treatment for 12 weeks prior to enrollment. After enrolling 24 subjects (12 in each group), 8 dropped out of the treatment group due to intolerance of taste and/or nausea prior to study completion. The final analysis revealed a mean decrease in Y-BOCS of 0.82 (95% confidence interval -1.62 to 0.01, $P = .053$) for each week that treatment continued. The authors note that 2 responders to treatment continued taking glycine for over a year with continued benefit.

A study[29] in 13 healthy male controls of 0.8 g/kg glycine given orally immediately prior to a battery of cognitive tests found no effect on measures of working memory, declarative memory, attention, or perceptual processing. The effect of glycine on cognitive tasks has been inconsistent, possibly related to differences in dosing and treatment conditions.[30-32]

In a study[18] of patients with chronic regional pain syndrome 1, intrathecal glycine was given to 19 patients eligible for intrathecal baclofen treatment in a double-blind placebo-controlled crossover study. The dose was started at 8 mg/24 h and increased weekly by 8 mg/24 h to 32 mg/24 h in the fourth week. Pain, movement disorders, activity, and global impressions of patients and clinicians were measured during 4 weeks of treatment with a 1-week washout period between treatments. There were no significant differences between the 2 groups. Drowsiness, headache, dysesthesia, and nausea and vomiting were the most frequently reported adverse effects and did not differ between groups.

D-Serine

An early placebo-controlled trial used D-serine to augment clozapine for the treatment of schizophrenia with D-serine given as 30 mg/kg/d for 6 weeks.[37] The results did not show any benefit to this agent versus placebo as measured by Clinical Global Impression, Positive and Negative Syndrome Scale (PANSS), Scale for the Assessment of Negative Symptoms (SANS), or Hamilton Depression Rating Scale (HDRS). Treatment-emergent adverse events were measured using the Simpson-Angus Rating Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes's Akathisia Rating Scale (BARS). There were no significant side effects in either group. Overall, these results were in contrast to the use of the partial agonist DCS, which negatively impacted the efficacy of clozapine. They were also contrary to an earlier study[38] adding D-serine 30 mg/kg/d to nonclozapine antipsychotics, which resulted in benefits to positive, negative, and cognitive symptoms while being well tolerated. Patients in this earlier trial were primarily treated with first-generation antipsychotics. A 6-week crossover study[39] in olanzapine and risperidone-treated patients replicated these findings with significant ($P < .001$) improvements in PANSS-negative, positive, and cognitive scores. A later 4-week dose-escalation study[40] suggested that doses $\geq$60 mg/kg/d may be more effective based on effect size of composite PANSS and a dose-by-time interaction.

D-serine 30 mg/kg/d was given to patients in a 6-week placebo-controlled crossover study[41] of 22 patients with

chronic symptoms of post-traumatic stress disorder (PTSD). Hamilton Anxiety and the Mississippi Scale for Combat-Related PTSD had significant reductions in the treatment arm versus placebo ($P=.007$ and $P=.001$, respectively), and reductions in the Clinician-Administered PTSD scale did not reach significance ($P=.07$). Nineteen of the patients were receiving pharmacotherapy, which included therapeutic doses of antidepressants.

D-Serine in Special Populations

Nine children with Tourette syndrome, ages 9 to 18 years, were given D-serine (max 30 mg/kg/d) for 6 weeks to evaluate the effect on tic suppression as determined by the Yale Global Tic Severity Scale, total tic score, and combined score.[42] These outcomes were compared against both a placebo arm (n = 5) and a treatment arm with the glutamate antagonist, riluzole (n = 10). There was no significant difference in combined score or total tic score between the D-serine and placebo arms (mean percentage improvement 39.5 vs 30.2, $P=.50$, and 25.0 vs 34.0, $P=.69$, respectively) or between riluzole and placebo arms (43.7, $P=.35$, and 38.0, $P=.85$).

D-Alanine

D-Alanine is a selective and potent endogenous ligand of glycineB site that is also regulated by DAAO and Asc-1. It was studied as adjunctive treatment for schizophrenia in 32 patients.[43] Fourteen out of the 32 patients received 100 mg/kg of oral D-alanine in orange juice for 6 weeks and were compared to placebo. The D-alanine group showed an 11% reduction in PANSS-total ($P<.0001$), 13% reduction in PANSS-positive ($P<.0001$), 12% reduction in PANSS-cognitive ($P=.0002$), and 17% reduction in SANS ($P<.0001$). Side effects measured by SAS, BARS, and AIMS were not significant and did not differ between groups. The apparent therapeutic dose of 100 mg/kg is consistent with the lesser potency of D-alanine compared with D-serine (with a therapeutic dose of 30 mg/kg/d) and with the intermediate bioavailability relative to glycine (therapeutic dose 800 mg/kg/d).[43,44]

Glycine-B Partial Agonists

In addition to the anti-infective DCS, which has been studied for a variety of psychiatric conditions and reviewed elsewhere, newer agents have been developed in this class in effort to promote NMDAR function without the subsequent receptor desensitization and internalization.[10,28] A single intravenous dose of the glycineB partial agonist GLYX-13 (rapastinel) was given to patients with major depressive disorder (MDD) who had not previously responded to treatment with biogenic amine antidepressants during the current episode.[45] Doses were 1, 5, 10, and 30 mg/kg. Symptoms improved based on the HDRS after 2 hours and persisted at day 7. This agent is moving into phase 3 trials based on this proof-of-concept study and another study with repeat dosing that showed sustained antidepressant efficacy.

Glycine-B Antagonists

A number of synthetic glycineB antagonists have been studied in a variety of clinical settings. These agents include gavestinel, licostinel, GV196771, and GW468816.

Overactivation of NMDAR produces elevated intracellular calcium and results in metabolic disturbances that lead to cell death. The glycineB site antagonist gavestinel (GV150526) was studied in a large randomized clinical trial of patients with acute stroke after determining safety and tolerability and positive results on infarct size in rats.[46] The Glycine Antagonists in Neuroprotection (GAIN) International trial randomized 1804 patients; 891 received the study drug and 897 received placebo. Patients were required to receive treatment within 6 hours of symptom onset. The primary end points were survival combined with the Barthel activities of daily living index at 3 months. There were no differences in any primary or secondary outcomes between study drug and placebo. The results of GAIN Americas showed similar negative outcomes.[47]

Licostinel

Licostinel is another glycineB antagonist that was studied in acute ischemic stroke although in a much smaller placebo-controlled trial.[48] Forty-four patients received escalating doses of licostinel infusion (up to 3 mg/kg). Although treatment also failed to separate from placebo, there were no major psychotomimetic effects or significant safety concerns. At higher doses (1.2 to 3 mg/kg), transient sedation, dizziness, and nausea were observed.

GW468816

In a newer line of research, the glycineB antagonist GW468816 was studied at a dose of 200 mg/d given for 5 weeks for the prevention of relapse in recently abstinent female smokers. This was based on evidence suggesting the role of NMDAR-mediated glutamatergic signaling mediating relapse and the observation that nonglycine NMDA antagonists alter dopamine release following administration of a variety of addictive drugs.[49,50] The investigators did not find any benefit from GW468816 in terms of abstinence rates, rate of relapse, or time to relapse. Plasma drug concentrations did not correlate to smoking outcomes or self-report of craving. There was a lack of side effects, which suggests the study drug may have been underdosed.

GV196771

GV196771 is a potent, selective glycineB antagonist that was studied in 63 subjects (32 received the study drug) with neuropathic pain in a randomized, double-blind, placebo-controlled, parallel-group fashion.[51] Patients were treated with GV196771 300 mg orally daily for 14 days followed by a 7-day washout period. There was no difference in spontaneous or evoked pain, quantitative sensory testing, or patient satisfaction between groups. Investigators speculated that poor central penetration might explain why these results did not replicate animal studies.

Kynurenic Acid

Kynurenic acid (KYNA) is an endogenous competitive antagonist at the glycineB site of NMDAR as well as a noncompetitive antagonist of α7 nAChRs. It is a product of tryptophan metabolism, dependent on kynurenine aminotransferase (KAT). Elevated levels of KYNA have been found in the prefrontal cortex and CSF of patients with schizophrenia and gives further support to the NMDA-hypofunction hypothesis of schizophrenia.[9] Reducing KYNA through inhibition of KAT represents a potential pharmacodynamic target related to glycine, and work in this field is growing. Most brain KYNA is produced by kynurenine aminotransferase II (KAT II), and preclinical work with inhibitors of KAT II has shown improvements in cognition in rats and nonhuman primates.[52] These agents have not yet reached human trials.

Alterations in tryptophan/kynurenine metabolism have also been implicated in MDD. The selective serotonin reuptake inhibitor (SSRI) escitalopram at doses of 20-40 mg/d given for 12 weeks to both healthy subjects and those meeting criteria for a major depressive episode was found to reduce the levels of neurotoxic kynurenine metabolites, 3-hydroxykynurenine, and quinolinic acid, the latter of which is an NMDAR agonist.[53] These changes in biomarkers occurred more slowly than improvement in depressive symptoms measured by HDRS and the Beck Depression Inventory. This is most likely a function of shifting tryptophan metabolism toward serotonin production and so may be a class effect of SSRIs.

Glycine Transporter 1 Inhibitors

Human clinical studies of GlyT1 inhibitors are summarized in the Table. These agents include bitopertin, GSK1018921, ORG-25935, and sarcosine (N-methylglycine). Inhibition of GlyT1 increases the amount of glycine in the synapse, and 50% occupancy of GlyT1 corresponds to a 2-fold increase in intrasynaptic glycine. Although phase 3 trials of bitopertin showed promise, development of this molecule has since been abandoned for schizophrenia.[59] As was seen with D-serine, the addition of sarcosine to clozapine did not provide additional benefit.[64] First-generation antipsychotics haloperidol, thioridazine, and chlorpromazine have been shown to inhibit glycine uptake by GlyT1, and clozapine and olanzapine did not.[68] Studies with additional compounds (R213129, R231857) found that GlyT1 inhibitors improve scopolamine-inducted impairments in psychomotor and cognitive function.[69,70]

Glycine Transporter 2 Inhibitors

The development of GlyT2 inhibitors has not yet resulted in published human studies. Work in this area has clarified the role of N-arachidonyl-glycine (NAGly), an endogenous fatty acid, structurally related to the endocannabinoid anandamide, which is a relatively selective GlyT2 inhibitor. Preclinical studies suggest that GlyT2 inhibitors would be useful in pain conditions.[71]

D-Amino Acid Oxidase Inhibitors

DAAO has been found to be overactive in schizophrenia with resultant low levels of D-serine.[72,73] As both D-serine and D-alanine are potent agonists of the glycineB site, increasing the concentrations of these molecules can increase the activity of NMDAR. Therefore, inhibiting DAAO, the enzyme responsible for metabolizing both D-serine and D-alanine, has become a drug target of interest.[74] Several DAAO inhibitors based on the weak prototype benzoic acid have been reported in the literature.[74,75]

In a randomized, double-blind, placebo-controlled clinical trial, patients with chronic schizophrenia, who had been stable for 3 months or more on antipsychotic therapy, showed 21% improved PANSS scores over placebo when treated with 1 g/d sodium benzoate (a DAAO inhibitor) as add-on therapy with little side effects attributed to sodium benzoate.[76] Patients were treated with both first- and second-generation antipsychotics. Another randomized, double-blind, placebo-controlled clinical trial showed statistically significant improvement in the Alzheimer's Disease Assessment Scale for cognitive function for patients with mild cognitive impairment or mild Alzheimer disease that received sodium benzoate therapy over placebo.[77]

There is some evidence suggesting that the antipsychotic risperidone inhibits DAAO, which may contribute to its efficacy in treating schizophrenia.[78]

Clozapine

Augmentation studies[34,79] with glycinergic agents to treat schizophrenia tend not to improve symptoms in clozapine-treated patients and often worsen them. This suggests that clozapine independently exerts some glycinergic activity. Clozapine has been shown to enhance the release of D-serine (as well as glutamate) from glial cells and leads to upregulation of NMDA receptors.[80] Some evidence suggests that clozapine exerts a direct partial agonist activity at the glycineB site itself.[81] It is also possible that lack of positive effect augmenting clozapine is related to the severity of illness as clozapine-treated patients often represent a treatment-resistant subpopulation with severe pathology.

Discussion

Pharmacological agents that modulate glycinergic transmission in the CNS present myriad opportunities for advancing therapeutic drug interventions. Because of both excitatory and inhibitory roles, variable baseline levels of

TABLE: Features of human studies of glycine transporter 1 inhibitors

Compound	Authors, Year	Intervention	Study Design (Duration)	Patient Population (Sample Size)	Results
ORG-25935	De Bejczy et al,[55] 2014	Oral, 12 mg bid, option to reduce to 8 mg bid if adverse effects	Multicenter, randomized, double-blind, placebo-controlled trial (12 weeks)	Detoxified alcohol-dependent patients N = 141 (intervention group, 75; placebo group, 66)	No difference in primary end point of percentage of heavy drinking days (14.7% vs 13.8%, $P = .41$), nor in any other relapse-related measure.
	Schoemaker et al,[56] 2014	Oral, 4 to 8 mg bid and 12 to 16 mg bid	Randomized, placebo-controlled trial (12 weeks)	Schizophrenia, predominant negative symptoms, treated with second-generation antipsychotics N = 214 (4-8 mg bid, 71; 12-16 mg bid, 73; placebo, 70)	No evidence of significant clinical benefits for either dose group on negative symptoms as measured by SANS.
	Nations et al,[57] 2012	Oral, 4 mg or 12 mg weekly for 3 weeks with CBT	Randomized, double-blind, placebo-controlled, parallel-group trial (5 weeks)	Panic disorder w/w/o agoraphobia N = 40 (4 mg, 11; 12 mg, 15; placebo, 14)	No statistically significant benefit for either dose over placebo on the primary end point (PDSS total score) or on any secondary efficacy end point. The 4-mg dose was better tolerated than 12 mg.
	D`Souza et al,[58] 2012	Oral, 16 mg on each test day (2 test days total, separated by a week)	Phase I, randomized, counter-balanced, within-subject, crossover design (2 weeks)	Healthy males; ketamine-induced psychotomimetic symptoms N = 12	Significantly reduced ketamine-induced peak increase in total PANSS scores ($P = .02$) and CADSS clinician-rated scores ($P = .0039$) with an effect size (Cohen d) of 0.71 and 0.98, respectively. VAS scores of *drowsy* ($P = .0068$) and *irritable* ($P = .043$) were significantly higher on the Org 25935 versus placebo.
GSK1018921	Ouellet et al,[59] 2011	Oral Part A: 0.5, 2, 5, 25, 70, 120, 200, 280 mg once Part B: 80 mg, 200 mg once	First-time-in-human, pharmacokinetics, safety and tolerability study, placebo controlled	Part A: Healthy subjects, N = 25 Part B: Healthy subjects who were regular smokers, N = 23	Dizziness, light-headedness, and visual disturbances were the dose-limiting adverse effects; the probability of developing dizziness was positively related to systemic exposure and increased with dose from 22% to 88% frequency in the 70- to 280-mg doses.
Bitopertin (RG1678)	Umbrict et al,[60] 2014	10, 30, or 60 mg/d	Randomized double-blind, placebo controlled trial (8 weeks)	Schizophrenia, predominant negative symptoms, treated with standard therapy N = 323 Placebo: 81 10 mg/d: 82 30 mg/d: 81 60 mg/d: 79	Significantly greater reduction in PANSS NSFS score in the 10-mg/d (−25%, $P = .049$) and 30-mg/d (−25%, $P = .03$) groups than in the placebo group (−19%). The mean reductions in the 60-mg group were comparable to placebo.
Sarcosine	Lane et al,[61] 2005	Oral, sarcosine: 2 g/d D-serine: 2 g/d	Randomized double-blind, placebo-controlled trial (6 weeks)	Schizophrenia acute exacerbation, treated with risperidone N = 65 (Sarcosine, 21; D-serine, 21; placebo, 23)	Sarcosine adjunctive group showed greater reduction in PANSS total scores in sarcosine group than the placebo ($P = .04$) and D-serine ($P < .001$) groups; similar results across other efficacy measures. No significant difference in D-serine adjunctive treatment versus risperidone alone in any efficacy domain.
	Lane et al,[62] 2010	Oral, sarcosine: 2 g/d D-serine: 2 g/d	Randomized double-blind, placebo-controlled comparison study (6 weeks)	Chronic schizophrenia, treated with atypical antipsychotics N = 60 (Sarcosine, 20; D-serine, 20; placebo, 20)	Sarcosine was superior to placebo based on PANSS total ($P = .005$), SANS ($P = .021$), QOL ($P = .025$), and GAF ($P = .042$) measures. D-Serine did not differ significantly from placebo in any measure.

TABLE: Features of human studies of glycine transporter 1 inhibitors (continued)

Compound	Authors, Year	Intervention	Study Design (Duration)	Patient Population (Sample Size)	Results
	Tsai et al,[63] 2004	Oral, 2 g/d	Double-blind, placebo-controlled trial (6 weeks)	Schizophrenia, treated with antipsychotics N = 38 (Sarcosine, 17; placebo, 21)	Sarcosine led to 17% reduction in PANSS-positive subscale, $P < .0001$ and a 14% reduction of the negative symptoms (SANS, $P < .0001$).
	Lane et al,[64] 2008	Oral, 1 or 2 g/d	Randomized, double-blind trial (6 weeks)	Schizophrenia, acutely symptomatic, antipsychotic-free N = 20 (2 g, 11; 1 g, 9)	No significant effect of dose. More patients in 2-g group responded based on 20% or more reduction of the PANSS total score.
	Lane et al,[65] 2006	Oral, 2 g/d	Double-blind, placebo-controlled trial (6 weeks)	Schizophrenia, treated with clozapine N = 20 (Sarcosine, 10; placebo, 10)	Both treatment arms were comparable in terms of effect on PANSS and all subscales. No difference in adverse effects measured by SAS, AIMS, or BARS.
	Tsai et al,[66] 2014	Oral, 2 g/d	Double-blind, placebo-controlled (8 weeks)	Parkinson disease with dementia N = 30 (Sarcosine, 15; placebo, 15)	Significant differences between groups in HDRS score ($P = .049$) at week 2 and Neuropsychiatry Inventory ($P = .039$) at week 4. Effects were greater and included significant effects on UPDRS ($P = .04$ at week 8) if advanced patients were excluded. Sarcosine did not exacerbate motor or cognitive features.
	Huang et al,[67] 2013	Oral, citalopram 20 mg or sarcosine 500 mg capsules Dose of sarcosine could be titrated	Randomized, double-blind, citalopram-controlled trial (6 weeks)	Major depressive disorder N = 40 (Citalopram, 20; Sarcosine, 20)	Sarcosine produced greater improvements in HDRS-17 (4.7, 4.6, and 5.3 at weeks 2, 4, and 6, $P = .009$, .021, and .012, respectively) and GAF (7.5, 10.1, and 9.6 at weeks 2, 4, and 6, $P = .004$, $<.001$, and .002, respectively) than citalopram throughout the study with effect sizes of 0.95 and 1.19 at the end of the study.
	Wu et al,[68] 2011	Oral, sarcosine 500 mg/d flexibly dosed to 2000 mg/d	Open-label, prospective (10 weeks)	Obsessive-compulsive disorder, Y-BOCS > 16 Drug-naïve, N = 8 Prior SSRI, N = 6 Adjunctive, N = 3	Y-BOCS scores decreased from 27.6 ± 5.8 to 22.7 ± 8.7, a mean decrease of 19.8% ± 21.7% ($P = .0035$). Eight (32%) subjects were regarded as responders (>35% reduction in Y-BOCS scores). Five responders by week 4. Well tolerated.

AIMS = Abnormal Involuntary Movement Scale; BARS = Barnes's Akathisia Rating Scale; CADSS = Clinician-Administered Dissociative States Scale; CBT = cognitive and behavioral therapies; GAF = Global Assessment of Functioning; HDRS = Hamilton Depression Rating Scale; NSFS = Negative Symptom Factor Score; PANSS = Positive and Negative Syndrome Scale; PDSS = Panic Disorder Severity Scale; QOL = quality of life; SANS = Scale for the Assessment of Negative Symptoms; SAS = Simpson-Angus Rating Scale; UPDRS = Unified Parkinson's Disease Rating Scale; VAS = visual analog scale; Y-BOCS = Yale-Brown Obsessive Compulsive Scale.

endogenous ligands, and the relatively quick adaptive response of NMDAR, universally effective agents have yet to be developed. New research into GlyT1 inhibitors, KAT inhibitors, DAAO inhibitors, and agents that modulate SRR and Asc-1 may eventually lead to viable compounds with novel actions that augment or offer alternatives to currently available therapeutics. This may happen sooner than previously thought as significant preclinical research with the drug rapastinel (GLYX-13), suggests a therapeutic strategy for a number of conditions that may provide benefit without desensitization or NMDAR internalization.[45,82,83] The drug was granted Breakthrough Therapy status by the Food and Drug Administration in late January of 2016 as a result of phase 2 trials for adjunctive treatment of major depression.[45]

Although the mental health clinician awaits these new drugs, it is important to note that glycine, D-serine, D-alanine, β-alanine, taurine, and sarcosine are available to patients through nutritional supplement vendors. Assessing patients' concomitant supplement use is always important during comprehensive medication review, and these seemingly innocuous amino acids and derivatives may easily be overlooked. In particular, β-alanine has become a popular ergogenic aid and is present in many workout supplements. Although there are no human

clinical trials of this agent for psychiatric indications, the neurologic side effect of paresthesia is well documented. Mental health clinicians should keep in mind the prodigious neurologic effects of the smallest amino acid, glycine, when treating patients.

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