

Glycine transporters in schizophrenia. A new hope or informational noise?

Przemysław Zakowicz^{1,2}, Joanna Pawlak¹

¹ Department of Genetics in Psychiatry, Department of Psychiatry,
Poznan University of Medical Sciences

² Treatment Center for Children and Youth in Zabór

Summary

Currently, we observe a huge number of publications describing the role of glycine transporter (GlyT1) inhibitors in schizophrenia treatment. The concept of application for these drugs derives from the glutamatergic theory of schizophrenia. This theory explains psychotic disturbances as the consequence of NMDA receptor functioning defect. The role of the mentioned receptor depends mostly on the presence of cofactors. One such cofactor is the simplest amino acid, glycine. This amino acid affects the glycine-binding site, located on the NR1 subunit of NMDAR and enables activation of the receptor. Substances enhancing the access of glycine to the receptor could hypothetically improve neuroplasticity. Higher efficacy of these neuroplastic processes may protect from cognitive deterioration and negative symptoms in the course of schizophrenia.

In this article we present a systematic review of current literature on the topic of GlyT1 inhibitors in schizophrenia treatment (the state of literature as of November 2019). Firstly, we described the preclinical reasons for glycine enhancement use. Next, we used CINAHL, EMBASE, EMCARE, Medline, PsycINFO, PubMed and Google Scholar databases to extract and analyze evidence from clinical trials. GlyT1 inhibitors seem to have a potential in searching for novel substances in the treatment of negative symptoms, but their capacity to reduce cognitive deficits is not evidenced. So far, the clinical efficacy of several substances was proven, including N-methylglycine (sarcosine), bitopertin and derivatives obtained with chemical synthesis. Some of these substances demonstrate a beneficial clinical effect, but the number of published reports in this area is disproportionate to the value of evidence.

Key words: schizophrenia, negative symptoms, glycine

Introduction

In the central nervous system, glycine serves the role of both a neurotransmitter and a neuromodulator [1]. The latter role is especially important in schizophrenia research

due to glycine's involvement in N-methyl-D-aspartate receptor (NMDAR) function, which takes part in synaptic plasticity and neural network learning [2]. Structurally, the NMDAR is a complex of subunits, including the glycine-binding site, which ensures proper receptor activity [3]. Correct function of the NMDAR requires maintaining a relatively constant concentration of glycine near excitatory synaptic endings. This condition is possible due to glycine transport system activity, based on two different proteins: glycine transporter type 1 (GlyT1) and glycine transporter type 2 (GlyT2) [1]. Both proteins belong to the sodium-dependent solute carrier family SLC-6. The former (GlyT1) is of particular interest in the area of antipsychotic medication. The use of pharmacological agents modulating NMDAR activity would be an attractive alternative for currently used neuroleptics, which generate a plethora of side effects. Despite promising outcomes of preclinical studies, the use of GlyT1 inhibitors in the treatment of schizophrenic patients still remains controversial.

Glycine in the glutamate theory of schizophrenia

Broad interest in the NMDAR derives from the similarity between psychodysleptic and entactogenic activity of NMDAR antagonists and psychotic symptoms. Such similarity was described for phencyclidine and ketamine. Intoxication with these substances leads to severe disturbances in orientation and hallucinations, especially visual, resembling symptoms observed in paranoid schizophrenia [4]. Despite the well-known role of dopamine and other monoamines that affect mainly subcortical neurotransmission, the question of the basis of thought association disturbances, tightly connected with language and cognitive deterioration (also in young age; dementia praecox) remains open [5]. Some explanation for the pathogenesis of schizophrenia is provided by mechanisms of cortical neural plasticity. Cognitive and linguistic disorganization suggests underlying altered connectivity between certain areas of neural networks, particularly those areas involved in language understanding, sensory perception (especially auditory) and areas that regulate proper motivation and volition. These phenomena reflect the results of neurochemical and neuroimaging studies [6] and find confirmation in insufficient synchronizing function of glutamatergic neurons [7].

The NMDAR plays a crucial role in information processing and synaptic activity in the central nervous system. Biochemically, it consists of different subunits, namely: NR1, NR 2A, 2B, 2C, 2D, and NR3 A and B [3]. Therefore, this receptor is not a unitary protein complex and its composition also varies between different brain regions. Moreover, neurodevelopmental changes in subunit composition of NMDA receptors have been described (neurodevelopmental switch) [8].

The concept of glutamatergic synaptic plasticity encompasses two main processes: long-term potentiation (LTP) and long-term depression (LTD). The LTP and LTD processes lead to metabolic changes in synaptic connections, which determines

the connection weight (speed and efficacy of its usage) [9, 10]. These changes occur under specific conditions that apply to the NMDAR activation itself. Functionally, the NMDAR is activated by glutamate, but it also requires cofactors, namely glycine site agonists [11].

Initial interest with the NMDAR was based on its direct antagonists, such as ketamine or phencyclidine (PCP). Unfortunately, these substances caused numerous side effects, e.g., disorders of consciousness, hallucinations, and affective disturbances, that could lead to worsening of the disease course [12]. Therefore, efforts were directed toward more specific target sites, such as the glycine site of the NMDAR and glycine transporters. This approach resulted in the discovery of novel drugs called glycine reuptake inhibitors. The first trials with a GlyT1 inhibitor, glycyldodecylamide (GDA), showed suppression of PCP-induced hyperactivity in rats. Further usage of specific antagonists on hippocampal slices confirmed an impact on NMDAR function [13].

Preclinical studies on animals suggest a beneficial effect of GlyT1 inhibitors, especially for cognitive models including prepulse inhibition and social functioning. The sarcosine derivate improves social recognition in rats, similarly to clozapine, hence the attempts of using GlyT1 inhibitors to improve negative symptoms in schizophrenia. Current treatment regimens, based mainly on monoamine neurotransmission, are not effective in restoring proper social functioning [14].

In this article we would like to present the outcomes of a systematic review, assessing the use of such substances in schizophrenic patients. We included only peer-reviewed clinical studies conducted on patients with a diagnosis of schizophrenia (excluding review papers and conference abstracts), retrieved using the databases: CINAHL, EMBASE, EMCARE, Medline, PsycINFO, and PubMed for English language materials and Google Scholar for articles in Polish. The research was made by entering the key words: (*GlyT1* OR *glycine transporter*) AND *schizophrenia*. The number of obtained records was 858 papers and after duplicate removal, 300 articles were accepted for title and abstract screening. Taking into account the inclusion criteria, 18 articles were selected for detailed full-text review. The model of systematic review was based on the PRISMA algorithm [15]. A comprehensive process of the review is depicted in Fig. 1. A summary of the most important clinical trials is presented in Table 1.

Table 1. Summary of clinical trials assessing the use of GlyT1 inhibitors in schizophrenic patients

Substance	Author and year of publication	Comparison	Period of clinical observation	Outcomes
N-methylglycine (sarcosine)	Tsai et al. 2004	Chronically ill patients treated with adjunctive sarcosine (n = 17) vs. patients treated with adjunctive placebo (n = 21)	6 weeks	Significant improvement of functioning in PANSS, SANS, and BPRS in sarcosine-treated group of patients
	Lane et al. 2005	Patients treated with risperidone and placebo (n = 23) vs. patients treated with risperidone and sarcosine (n = 21) vs. patients treated with risperidone and D-serine (n = 21)	6 weeks	Significant improvement of functioning in PANSS and SANS in sarcosine-treated group of patients
	Lane et al. 2006	Patients treated with clozapine and sarcosine (n = 10) vs. clozapine and placebo (n = 10)	6 weeks	No beneficial effect of treatment augmentation
	Lane et al. 2008	Patients without antipsychotic management, in acute episode of the disease. After introduction of sarcosine in the dose of 1g (n = 9) and 2 g (n = 11)	6 weeks	Significant improvement of symptoms in PANSS in sarcosine-treated group of patients
	Lane et al. 2010	Chronically ill patients treated with adjunctive sarcosine (n = 20) vs. chronically ill patients treated with adjunctive D-serine (n = 20) vs. chronically ill patients treated with adjunctive placebo (n = 20)	6 weeks	Significant improvement of functioning in PANSS and SANS in sarcosine-treated group of patients
	Amiaz et al. 2015	Clinically-stable patients. Additional treatment with sarcosine in doses of 2g (n = 5) vs. 4 g (n = 17)	8 days	Improvement in positive and general symptoms in PANSS in sarcosine-treated group of patients
	Lin et al. 2017	Chronically ill patients treated with adjunctive sarcosine (n = 21) vs. treated with adjunctive sarcosine and sodium benzoate (n = 21) vs. treated with adjunctive placebo (n = 21)	12 weeks	Improvement in GAF in sarcosine – and sodium benzoate-treated patients

dalszy ciąg tabeli na następnej stronie

Bitopertin	Umbricht et al. 2014	323 schizophrenic patients with predominant negative symptoms. Treated with adjunctive bitopertin at doses of 10 mg vs. 30 mg vs. 60 mg vs. adjunctive placebo	8 weeks	Significant reduction of negative symptoms in patients treated with bitopertin
	Bugarski-Kirola et al. 2017	605 patients treated with adjunctive placebo or bitopertin in two doses (5 mg vs. 10 mg): DayLyte 594 patients treated with adjunctive placebo or bitopertin in two doses (10 mg vs. 20 mg): FlashLyte	24 weeks	Reduction of symptoms in PANSS; no significant advantage over placebo
ORG-25935	Schoemaker et al. 2014	Clinically-stable patients (n = 215), treated with adjunctive ORG-25935 in doses of 4-8 mg vs. 12-16 mg vs. placebo	12 weeks	No significant difference among groups in PANSS, GAF and SANS assessment
AMG 747	Dunayevich et al. 2017	Clinically-stable patients (n = 153) treated with adjunctive AMG 747 in doses of 5 mg vs. 15 mg vs. 40 mg vs. placebo	12 weeks	Significant reduction of negative symptoms in the group treated with 15 mg in comparison with placebo

Outcomes of the systematic review of literature

N – methylglycine (sarcosine)

N-methylglycine is both a selective ligand for the glycine site of the NMDA receptor and an antagonist of GlyT1. Similarly to D-alanine, it is not involved in other neurotransmission systems. In the provided time frame (state of literature as of November 2019), we found 10 published clinical trials, describing the use of sarcosine in patients with a diagnosis of schizophrenia. The first placebo-controlled trial of sarcosine was conducted on a small group of chronically ill patients. Patients diagnosed with schizophrenia who were on stable antipsychotic doses during three months of treatment prior to the study were included. The 38-patient study was double-blinded and randomized into two therapeutic arms: 17 patients treated with sarcosine versus 21 in placebo group. Adding sarcosine to the treatment resulted in significant improvement of positive, negative and cognitive symptoms, measured with the following psychometric scales: *Positive and Negative Symptoms Scale* (PANSS), *Scale for the Assessment of Negative Symptoms* (SANS) and the *Brief Psychiatric Rating Scale* (BPRS) [16]. In further research, the study group was enlarged. Patients with an acute exacerbation of schizophrenia (n = 65) were divided into three treatment groups: risperidone + pla-

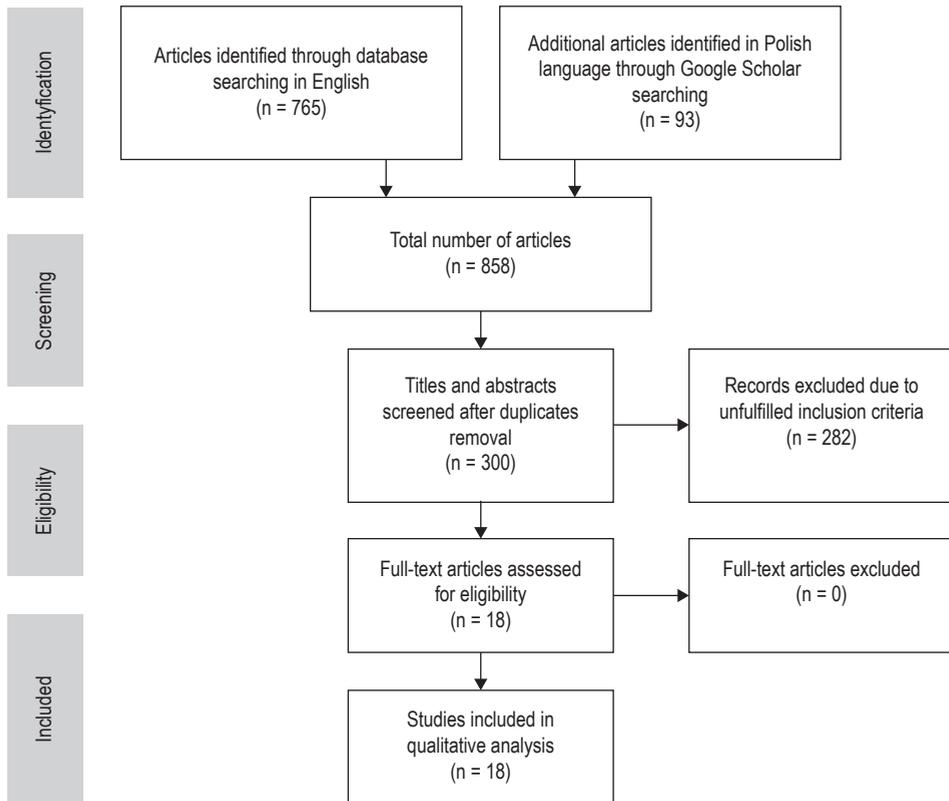


Fig. 1. Systematic review: using the key words (GlyT1 OR Glycine transporters) AND schizophrenia, CINAHL, EMBASE, EMCARE, Medline, PsycINFO, and PubMed databases were searched for English language articles; moreover, Polish language articles were included, indexed in the Google Scholar database (n = 93). State of literature as of November 2019. Among the obtained articles, 18 were assessed for eligibility and included in the analysis.

cebo (n = 23), risperidone + D-serine (n = 21), and risperidone + sarcosine (n = 21) [17]. In the sarcosine group, significant clinical improvement was observed in PANSS and SANS, as compared with the other groups. The results indicate a lower efficacy of D-serine than sarcosine. A subsequent study confirmed these results [18].

However, the study of Lane et al. did not confirm a beneficial effect of treatment augmentation with sarcosine in clozapine-treated patients compared with the placebo group [19]. Sarcosine was also tested in monotherapy. Patients not on neuroleptics (n = 20) were treated with two different doses of sarcosine: 2 g/day (n = 11) versus 1 g/day (n = 9). In both groups, significant improvement in positive, negative and general symptoms in PANSS was observed [20]. The results obtained by Amiaz et al. confirmed the efficacy of sarcosine after a shorter treatment time (8 days), but at

a higher dose (4 g/day) [21]. A study was also conducted assessing combined therapy with sarcosine and a D-amino acid oxidase inhibitor (sodium benzoate) in chronically ill schizophrenic patients [22]. Subjects (n = 63) in stable clinical state were divided into a placebo group (n = 21), sarcosine group (n = 21), and sarcosine plus sodium benzoate group (n = 21). After a 12-week trial of pharmacotherapy, patients were assessed with PANSS, the *Global Assessment of Functioning Scale* (GAF) and the *Clinical Global Impression-Severity Scale* (CGI-S). Cognitive functions were evaluated with the *MATRICES Consensus Cognitive Battery* (MCCB) tests. The sarcosine plus sodium benzoate group achieved improvement in the GAF scale, but there was no significant difference in PANSS and CGI-S scores between groups. For cognitive performance, the sarcosine plus sodium benzoate group had improved global composite cognition, verbal learning and memory. In the group treated with sarcosine alone, the ability to reason and problem solve significantly improved compared to the placebo group [22].

Neuroimaging studies conducted by Strzelecki et al. showed the impact of a six-month treatment augmentation with sarcosine on metabolite concentration in the dorsolateral prefrontal cortex (DLPFC) [23]. Three different markers were assessed: N-acetylaspartate (NAA); complex of glutamate, glutamine and GABA (Glx); and myo-inositol (mI). After treatment, NAA and Glx levels decreased, accompanied by a significant increase in mI level. In another trial, Strzelecki et al. also confirmed the differences in NAA and Glx levels in frontal lobe white matter [24] and the hippocampus [25] in sarcosine-treated patients.

Bitopertin

Bitopertin is a selective, non-competitive GlyT1 inhibitor, developed and clinically tested for the reduction of negative and cognitive symptoms in schizophrenia [26]. Initial results were promising: the substance was effective in animal studies as well as in human preclinical pharmacokinetic studies [27]. The outcomes of the second-phase clinical trials revealed a significant reduction in negative symptoms as measured by the PANSS [28]. However, a multicenter third-phase clinical trial did not demonstrate a beneficial effect. Two multicenter, double-blind, randomized, placebo-controlled trials (DayLyte and FlashLyte) conducted on 605 and 594 patients, respectively, showed a significant reduction in symptoms in PANSS [29] after 24 weeks of treatment with bitopertin 5 mg, 10 mg (DayLyte) and 10 mg, 20 mg (FlashLyte). However, the obtained results were not significantly better than in the placebo group. The nomenclature proposed by the European College of Neuropsychopharmacology (ECNP) lists bitopertin as a glycine reuptake inhibitor with no licensed indications. The efficacy of reduction of negative symptoms is described in cases where bitopertin is used together with antipsychotics. The side effects mentioned in the ECNP nomenclature include dizziness, nausea, and blurred vision [30].

ORG-25935

ORG-25935 is a synthetic substance that contains in its chemical structure the residue of N-methylglycine (sarcosine), which is responsible for the properties of selective inhibition of GlyT1. This drug was used as an augmentation strategy for neuroleptic treatment and was well tolerated in the administered doses (4-16 mg 2x/day). ORG-25935 was added to second-generation antipsychotic treatment in clinically stable patients. In the study by Schoemaker et al., 215 subjects were divided into three therapeutic arms: 4-8 mg twice daily, 12-16 mg twice daily, and a placebo group. After 12 weeks of treatment, 187 patients were assessed with PANSS, GAF and SANS, but no significant difference was observed between the groups [31].

AMG 747

AMG 747 is another synthetic selective GlyT1 inhibitor. In the second phase of clinical studies, clinically-stable patients were randomized into four groups receiving, respectively: 5 mg, 15 mg, 40 mg daily and placebo for 12 weeks. In 153 patients, psychometric assessment was performed using: *Negative Symptom Assessment* (NSA-16) and PANSS for negative symptoms, PANSS for positive symptoms, CGI-S and CGI-I for rating illness severity, and MATRICS (MCCB) or CogState Schizophrenia Battery (CSB) for cognitive functions. The group receiving 15 mg of AMG 747 showed a significant decrease in negative symptoms compared to the placebo group. Positive and cognitive symptoms did not show significant improvement after treatment [32].

PF-03463275

Thus far, the efficacy of this substance was assessed in clinical trials using neuroimaging. The ability to bind GlyT1 was confirmed in positron emission tomography (PET). For particular doses (10 mg, 20 mg and 40 mg daily), researchers observed proportional GlyT1 binding occupancy. The drug enhanced LTP in the schizophrenic group, with a higher binding rate observed in subcortical structures (basal nuclei) than in cortical regions. This drug, similarly to the one mentioned above, exhibits the clinical response in an inverted U-shaped model (best response at medium doses). PF-03463275 was well tolerated at the administered doses; however, it did not attenuate the ketamine-induced cognitive deficits [33].

Conclusions

Negative and cognitive symptoms remain the most important clinical challenge in the current therapeutic approach of schizophrenia. Treatment preventing cognitive

deterioration in patients could improve the prognosis and the quality of life. Understanding the relationship between the NMDAR and glycine underlies the development of novel leading substances with potential clinical significance in schizophrenia.

Selective glycine reuptake inhibitors increase the availability of this amino acid for the glycine-binding site of the NMDAR. This action may potentially increase the activity of the receptor. A further effect could be improved efficacy of synaptic plasticity processes, i.e., the basic mechanism of neuronal learning. However, substances acting directly on the NMDAR remain controversial because this receptor is not a unitary protein complex, conversely to other receptors studied in schizophrenia. The NMDAR types differ depending on the location in the central nervous system and on the stage of brain development. This makes the NMDAR very heterogenic, which creates challenges in the field of developing drugs that act on specific target sites. Moreover, the participation of this receptor in the phenomenon of excitotoxicity limits the use of its agonists [7]. Drugs bypassing the direct activation of the NMDAR, e.g., in the glycinergic mechanism, could be safer in clinical practice. The presented outcomes of the systematic review do not provide sufficient evidence for the efficacy of GlyT1 inhibitors.

Among the 18 cited studies, only 6 presented supportive findings. Treatment outcomes in small groups of patients are promising, but are not confirmed in larger populations. It is also worthwhile to notice that the use of psychometric scales in the assessment of symptom reduction remains controversial because of the categorization of symptoms [34]. Most of the retrieved articles were reviews or were based on pre-clinical studies. Therefore, the number of publications on this topic is disproportionate to the quality of evidence for clinical efficacy. Referring to our title, we are undoubtedly dealing with the effect of informational noise. It hinders the production of good quality evidence and gives an illusionary belief about the high level of knowledge in the area of GlyT. Explicitly, GlyT1 inhibitors provide hope for effectiveness, but the currently available clinical evidence is not sufficient to include these substances among antipsychotics.

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Address: Przemysław Zakowicz
Poznan University of Medical Sciences
Department of Psychiatry
Department of Genetics in Psychiatry
60–806 Poznań, Rokietnicka Street 8
e-mail: przemek@zakowicz.eu