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ARTICLE

Plasma glycine and serine levels in schizophrenia compared to normal controls and major depression: relation to negative symptoms

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Abstract

Previous studies have suggested decreased *N*-methyl-D-aspartate (NMDA)-type glutamate receptor function may contribute to increased negative symptoms in patients with schizophrenia. Consistent with this hypothesis, glycine, a co-agonist at NMDA receptors, has been reported to improve negative symptoms associated with the illness. This study was performed to determine if plasma levels of glycine or its ratio to serine, a precursor of glycine, are decreased in patients with schizophrenia compared to normal control subjects or patients with major depression. We also tested the hypothesis that these amino acids were correlated with negative symptoms in subjects with schizophrenia. Plasma levels of glycine, serine, and their ratio, were compared in 144 patients with schizophrenia, 44 patients with major depression, and 49 normal control subjects. All subjects were medication-free. Psychopathology was evaluated using the Brief Psychiatric Rating Scale (BPRS). Plasma glycine levels and glycine/serine ratios were decreased in patients with schizophrenia relative to control subjects and patients with major depression. By contrast, serine levels were increased in patients with schizophrenia compared to normal subjects but not compared to major depression. Patients with major depression also had increased plasma serine levels and decreased glycine/serine ratios compared to normal controls, but glycine levels were not different from those of normal controls. In subjects with schizophrenia, glycine levels predicted the Withdrawal–Retardation score (BPRS), whereas no such correlation was found in subjects with major depression. These results provide additional evidence that decreased availability of glycine may be related to the pathophysiology of negative symptoms. The decreases in plasma glycine levels support the evidence for an abnormality in the glutamatergic system in schizophrenia, and provide additional support for efforts to improve negative symptoms by augmentation of antipsychotic drugs with agonists at the glycine site of the NMDA receptor.

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Key words: Amino acids, glycine, glutamate, negative symptoms, NMDA, schizophrenia, serine.

Introduction

Recent investigations of the aetiology of schizophrenia have focused on hypofunction of *N*-methyl-D-aspartate (NMDA)-type glutamate receptors due, in part, to clinical evidence that phencyclidine, a non-competitive antagonist at the NMDA receptor, produces or exacerbates symptoms which bear some relationships with schizophrenia in normal controls and patients with this disease (Coyle, 1996; Farber et al., 1999; Goff and Coyle, 2001; Goff and Wine, 1997; Javitt and Zukin, 1991; Jentsch and Roth, 1999).

Glycine, which is an obligatory co-agonist at NMDA receptors, and thus, increases glutamatergic neurotransmission, as well as the glycine precursor serine, are amino acids that have drawn particular attention in research on schizophrenia and major depression

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(Farber et al., 1999; Lucca et al., 1993; Maes et al., 1995; Toru et al., 1994; Waziri et al., 1993). Glycine enhances activation of the NMDA-gated voltage-dependent cation channel via actions at strychinine-insensitive excitatory glycine sites (Gly-B) (D'Souza et al., 2000). Glycine transporters in synaptic membranes may modulate the concentration of glycine at NMDA receptors (Goff et al., 1999b). Metabolism of glycine, including its production from serine, is subject to action of the enzyme serine-hydroxymethyltransferase (SHMT) and the glycine cleavage enzyme system (GCS) (D'Souza et al., 2000). Activity of SHMT in subjects with schizophrenia has been reported to be deficient in some (Baruah et al., 1993; Waziri et al., 1993) but not all (Lucca et al., 1993) studies. Plasma levels of glycine and serine have been studied in normal subjects and patients with various psychiatric disorders to clarify the influence of diagnosis, age, sex, diet, stress, and hormonal changes (Waziri et al., 1984; Wilcox et al., 1985). There is evidence that venous plasma and CSF levels of amino acids, including glycine and serine, are significantly correlated in human subjects (D'Souza et al., 2000; Hagenfeldt et al., 1984; McGale et al., 1977), indicating that plasma levels of these amino acids reflect, to some extent, those in the central nervous system. Peroral administration of glycine has been shown to increase brain glycine levels both in rodents and humans (D'Souza et al., 2000; Javitt et al., 1994; Toth and Lajtha, 1986).

Studies of plasma or serum levels of serine in schizophrenia have produced inconsistent results. Several authors report elevated plasma or serum serine levels in patients with schizophrenia or related psychotic disorders (Baruah et al., 1991, 1993; Macciardi et al., 1990; Waziri and Mott, 1986; Waziri et al., 1983, 1984; Wilcox et al., 1985) while other investigators (Fekkes et al., 1994; Perry and Hansen, 1985; Rao et al., 1990) do not. Increased plasma serine levels have also been reported in subjects with major depression (Maes et al., 1995). There are also several studies that have investigated blood levels of glycine in schizophrenia (Baruah et al., 1991, 1993; Lucca et al., 1993; Macciardi et al., 1990; Perry and Hansen, 1985; Rao et al., 1990). While some have found normal blood glycine levels (Macciardi et al., 1990; Perry and Hansen, 1985; Rao et al., 1990), others reported increased concentrations (Baruah et al., 1991, 1993). The use of limited sample numbers may have confounded the results of these previous studies. In view of clinical evidence (Heresco-Levy et al., 1996, 1999; Leiderman et al., 1996) that adjunctive treatment with peroral glycine, by elevating blood levels, improves some types of clinical symptoms, especially negative symptoms, but not positive symptoms, a decrease in the plasma glycine concentration would be consistent with the hypoglutamatergic hypothesis of schizophrenia. Also, it was found that low pretreatment serum glycine levels predict negative symptoms improvement following glycine treatment (Heresco-Levy et al., 1996, 1999).

Only a limited number of attempts have been made to relate plasma levels of glycine and serine to psychopathology in patients with schizophrenia (Waziri et al., 1983; Wilcox et al., 1985). Wilcox et al. (1985) found correlations between a sum of seven items related to positive symptoms (conceptual disorganization, mannerism and posturing, grandiosity, suspiciousness, hallucinations, unusual thought), or negative symptoms (blunted affect) from the Brief Psychiatric Rating Scale (BPRS), and plasma serine or serine/glycine ratios in 12 psychotic patients, including four with schizophrenia. Waziri et al. (1983) reported that the plasma serine/cysteine ratio positively correlated with gross psychopathology in psychiatric patients, which included 14 with schizophrenia. These previous preliminary results indicate the need for clarification of the role of glycine and serine in the development of psychotic symptoms in a larger number of subjects with schizophrenia. In this respect, we hypothesized that decreased glycine availability, as indicated by lower than normal plasma levels of this amino acid, would be correlated with negative symptoms in patients with schizophrenia.

The aims of this study were to determine: (1) whether plasma glycine levels and the glycine/serine ratio are decreased in patients with schizophrenia compared to normal control subjects or patients with major depression and (2) if there is a correlation between glycine or serine levels or the glycine/serine ratio, and negative symptoms in subjects with schizophrenia.

Materials and methods

A total of 144 patients meeting DSM-III-R criteria for schizophrenia ($n=129$) or schizoaffective disorder ($n=15$; depressive 12, manic 1, unknown 2) (APA, 1987), 44 patients with major depression and 49 psychiatrically normal control subjects participated in the study. Subjects were interviewed with the Schedule for Affective Disorders and Schizophrenia Lifetime and Change (SADS-C) versions (Endicott and Spitzer, 1978). A psychiatric and treatment history was obtained from the subject, informants, and medical records. Subjects with current history of substance abuse or dependence, seizure or head injury were excluded from the study. Eligible patients had a complete physical examination. Standard laboratory testing was

Table 1. Demographic profiles of subjects

	Schizophrenia ($n=144$)	Major depression ($n=44$)	Normal controls ($n=49$)
Male/female	105/39	26/18	26/23
Age (yr)[a]	33.5 (9.4)	36.3 (11.1)	27.9 (8.2)
Duration of illness	12.3 (8.0)	13.7 (10.7)	–
In-patients/outpatients	109/35	20/24	–
BPRS Total score	28.8 (12.3)	20.0 (9.3)	–

Values represent mean (S.D.).
BPRS, Brief Psychiatric Rating Scale.
[a] Significant main effect of diagnosis [$F(2, 234)=9.12$, $p<0.001$].

normal. Clinical staff explained the nature of the study to the subjects, the risks and benefits, and the option not to participate in research. If the mental status of a subject was impaired to the point where s/he could not understand the nature of the study, its risks and benefits, or the option not to participate, the subject was not approached to be in research. This protocol was approved by Institutional Review Board of University Hospitals of Cleveland. After complete description of the study to the subjects, written informed consent was obtained. Demographic data of the subjects are presented in Table 1.

All patients with schizophrenia were withdrawn from psychotropic medication (38 had been treated with atypical antipsychotic drugs) except for an occasional dose of benzodiazepines or chloral hydrate for a minimum of 7 d [mean (S.D.) = 16.6 (10.2) d] before blood was sampled, based on the protocol reported elsewhere (Sumiyoshi et al., 1997a,b). No subjects had been treated with depot neuroleptics. If patients showed deterioration during the medication-free period, they were given active treatment immediately (Sumiyoshi et al., 2003). The BPRS, 18-item version (Overall and Gorham, 1962) (0–6 scale) was assessed at the time of blood sampling by trained research assistants with intra-class correlation coefficients of more than 0.8 (Sumiyoshi et al., 1997a,b). All patients with major depression had not received antidepressants or other psychotropic drugs for at least 3 months prior to the study due, mainly, to non-compliance. The Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) scores (mean $\pm$ S.D.) in these subjects at the time of assessment was 23.5 ± 9.8.

Blood sampling procedure was described in previous reports (Sumiyoshi et al., 1997a,b). Briefly, blood samples were obtained between 09:30 and 10:00 hours, 60 min after insertion of an in-dwelling venous catheter following an overnight fast. The overnight fasting for patients was supervised. This sampling was done concurrently with other test procedures (Sumiyoshi et al., 1997a,b). Physical exercise, alcohol, and caffeine were restricted for all the subjects during the study period.

Plasma levels of glycine and serine were measured using a high performance liquid chromatography with a Waters Pico-Tag column with the intra-assay and inter-assay coefficients of variation of 5% or less, based on an established method (Waters Associates, 1984).

Statistical analysis

Comparisons of plasma amino-acid levels and their ratios between subjects with schizophrenia, those with major depression, and normal controls were made using analysis of covariance (ANCOVA). When a significant main effect of diagnosis was found, subsequent post-hoc analysis was conducted. Multiple regression analyses were conducted to predict the psychopathology scores from age and one of the three measures of plasma amino acids (glycine and serine levels, and glycine/serine ratio) for the schizophrenia group. Effect sizes (ES) were calculated by the method of Cohen (1977). Significance was considered when the p value was less than 0.05. Values are expressed as mean (S.D.) unless specified otherwise.

Results

There was a significant main effect of age among the three groups [$F(2, 234)=9.12$, $p<0.001$] due to higher mean age for subjects with schizophrenia ($p<0.001$) and major depression ($p<0.0001$), compared to normal control subjects. There was a positive correlation between duration of neuroleptic-washout period and plasma serine levels in subjects with schizophrenia (Pearson; $r=0.38$, $p=0.0002$), indicating an effect of residual neuroleptic treatment to decrease serine levels. However, no such association was found for plasma glycine levels ($r=0.13$, $p=0.23$). ANCOVA (age as

covariate) revealed significant main effects of diagnosis on glycine [$F(2, 224) = 15.16$, $p < 0.0001$] and serine [$F(2, 224) = 3.00$, $p = 0.05$] levels, as well as the glycine/serine ratio [$F(2, 220) = 24.74$, $p < 0.0001$]. Post-hoc analyses indicated: (1) plasma glycine levels in patients with schizophrenia were lower than those in normal control subjects ($p < 0.0001$, ES = 0.94) and patients with major depression ($p < 0.01$, ES = 0.57) (Figure 1a); (2) subjects with either schizophrenia ($p < 0.05$, ES = 0.36) or major depression ($p < 0.05$, ES = 0.44) showed higher serine levels than did normal controls (Figure 1b); and (3) glycine/serine ratio in patients with schizophrenia was significantly less than those in normal controls ($p < 0.0001$, ES = 1.29) and subjects with major depression ($p < 0.001$, ES = 0.50), the latter also demonstrating a lower ratio than the normal controls ($p < 0.05$, ES = 0.80) (Figure 1c). Thirty-six per cent of subjects with schizophrenia showed a glycine/serine ratio that was below the 95% lower confidence interval (CI) for this ratio in normal controls. For all three measures, the main effect of sex was not significant [$F(1, 224) = 0.12$, $p = 0.73$; $F(1, 224) = 0.34$, $p = 0.56$; and $F(1, 220) = 0.25$, $p = 0.62$ respectively]. There were no significant difference in glycine or serine levels, or their ratio, between 129 patients with schizophrenia and 15 subjects with schizoaffective disorders (data not shown).

The BPRS Withdrawal–Retardation scores (emotional withdrawal, motor retardation, blunted affect), but not the BPRS Total or Positive scores, were predicted by plasma glycine levels, but not age ($p = 0.246$), in subjects with schizophrenia (Table 2), while no such association was found with serine levels or glycine/serine ratio. There was no significant correlation between glycine or serine levels, or the glycine/serine ratio, and the BPRS Total, Positive or Withdrawal–Retardation, or the HDRS scores in subjects with major depression (data not shown).

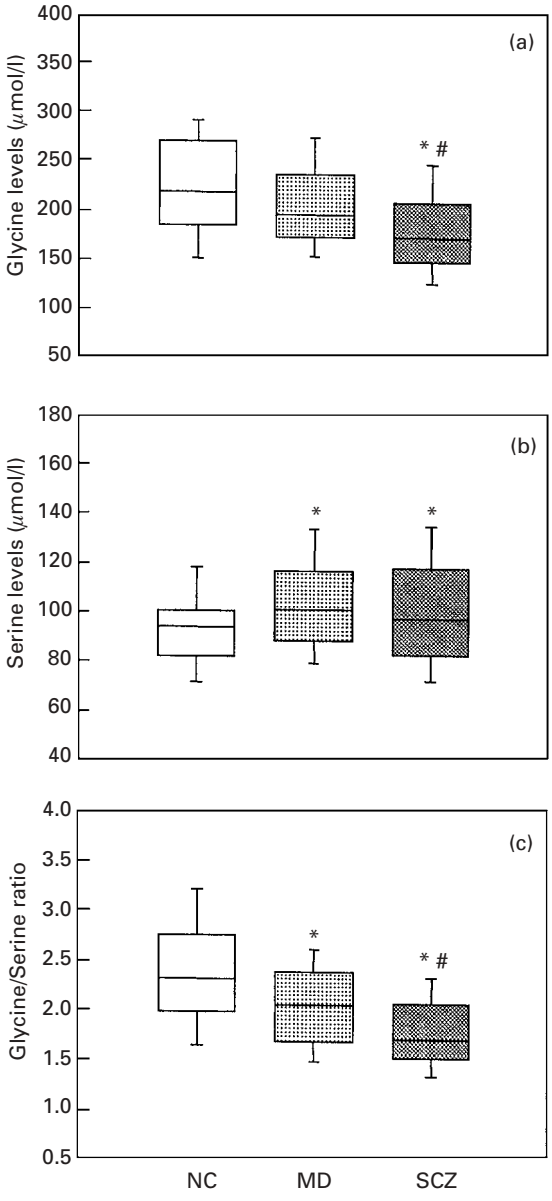

Figure 1. Box plots for (a) plasma glycine levels, (b) serine levels and (c) glycine/serine ratios. The line in the box represents median values. The top and bottom of the boxes are upper and lower quartiles respectively. Bars represent 90 and 10 percentiles. NC, normal controls ($n = 49$); MD, major depression ($n = 44$); SCZ, schizophrenia ($n = 144$). * Significantly different from controls subjects; # significantly different from patients with major depression (see text).

Discussion

This study provides, to our knowledge, the first evidence for decreased plasma glycine levels in patients with schizophrenia compared to control subjects or patients with major depression. Plasma serine levels, on the other hand, were found to be elevated in both subjects with schizophrenia and those with major depression. The mean values of plasma glycine and serine levels, as well as their ranges, in control subjects in the current study (Figure 1) are comparable to those reported in previous studies (D'Souza et al., 2000; Macciardi et al., 1990; Perry and Hansen, 1985; Smeraldi et al., 1987). Glycine/serine ratios decreased in the order: normal controls > major depression > schizophrenia. There were some significant correlations between amino-acids measures and severity of negative symptoms in subjects with schizophrenia.

Some previous studies with smaller numbers (15–27) of neuroleptic-free subjects with schizophrenia

Table 2. Relationship between plasma glycine levels and psychopathology

	Glycine		Regression analysis			
BPRS measure	β	p	r	F	d.f.	p
Total	−0.03	0.236	0.150	1.45	2, 125	0.240
Positive	−0.02	0.166	0.234	3.63	2, 125	0.029
Withdrawal–Retardation	−0.02	0.004	0.264	4.79	2, 125	0.010

BPRS, Brief Psychiatric Rating Scale.

have reported increased plasma glycine levels (Baruah et al., 1991, 1993). The plasma glycine levels for normal control subjects in those studies ranged from 160 to 200 μmol/l, lower than the mean levels of 223.5 μmol/l in our study. Differences in the sample numbers, method of determination of plasma glycine, or other unknown factors might be responsible for the discrepancy between these former reports and the current study, which included 144 patients. In fact, more than one-third of subjects with schizophrenia showed a glycine/serine ratio that was below the bottom of the 95% CI for this ratio in normal controls. The significant difference in plasma glycine levels between patients with schizophrenia and those with major depression reported here suggests that the decrease in this measure is specific to the former disorder. Further study with larger samples of subjects, and identification of the key influences on plasma glycine levels, are needed before it can be determined if plasma glycine levels have any usefulness as a biological marker for schizophrenia. At least, the absence of a significant correlation between the duration of the neuroleptic withdrawal period and plasma glycine levels in subjects with schizophrenia argues against a possible effect of residual medication on glycine levels.

As mentioned above, the increase in plasma serine levels in subjects with schizophrenia is consistent with most previous investigations (Baruah et al., 1991, 1993; Macciardi et al., 1990). Higher than normal concentrations of serine have also been found in specific brain regions of subjects with schizophrenia (Waziri et al., 1993). Peroral loading with serine produced psychotic symptoms in subjects with metabolic diseases (Pepplinkhuizen et al., 1980). Moreover, treatment with neuroleptic drugs was reported to decrease plasma serine levels in psychotic patients, including those with schizophrenia (Waziri and Mott, 1986), consistent with a positive correlation between duration of neuroleptic-withdrawal period and plasma serine levels, as reported here. This latter finding indicates that even greater plasma serine levels and smaller glycine/serine ratios would have been expected in subjects with schizophrenia after more prolonged duration of a neuroleptic-free period.

That subjects with major depression showed increased plasma serine levels is consistent with an independent report that studied a larger number of depressive subjects (Maes et al., 1995). This result, and the lack of significant difference in plasma glycine levels between patients with major depression and normal control subjects, accounted for the smaller glycine/serine ratio for the former group (Figure 1). Decreased plasma glycine levels in subjects with schizophrenia, along with increased serine levels, accounted for the decreased glycine/serine ratio for this group compared to the depressed subjects.

The negative correlations between plasma glycine levels and the BPRS Withdrawal–Retardation scores in subjects with schizophrenia suggest that the decreased availability of glycine contributes to the development of negative symptoms in schizophrenia. The lack of such correlation in subjects with major depression may indicate this mechanism is specific to schizophrenia. It has been found that the glycine-modulating site on the NMDA receptors in the brain is not fully saturated under physiological conditions (Farber et al., 1999). This contributed to the rationale for clinical trials to test the ability of adjunctive therapy with an agonist at this receptor site to improve negative symptoms in patients with schizophrenia (see Goff and Coyle, 2001 for review). Thus, glycine (Heresco-Levy et al., 1996, 1999; Javitt et al., 1994), D-serine (Tsai et al., 1998) or cycloserine (Goff et al., 1995, 1996, 1999b) have been found to improve negative symptoms, as well as some types of cognitive dysfunction, in patients with schizophrenia treated with typical antipsychotic drugs. These lines of clinical evidence, suggestive of a hypoglycinergic state in schizophrenia, are consistent with decreased plasma glycine levels and its association with the severity of negative symptoms in subjects with this disorder, as first demonstrated in the current study. Future studies determining if basal and post-treatment

plasma glycine levels predict negative symptom response to supplementation with glycine agonist compounds are indicated.

Adjunctive treatment with the glycine agonists, glycine (Heresco-Levy et al., 1996, 1999; Javitt et al., 1994), D-cycloserine (Goff et al., 1995, 1999b), and D-serine (Tsai et al., 1998), have been shown to improve negative symptoms in patients treated with typical antipsychotics. Of note is the fact that glycine selectively improves negative symptoms, but not positive symptoms or general psychopathology, when added to typical antipsychotic drugs (Javitt et al., 1994), providing further support for selective association between negative symptoms and plasma glycine levels. On the other hand, these glycine agonists do not improve (glycine, D-serine; full agonists) (Leiderman et al., 1996; Potkin et al., 1999; Tsai et al., 1999), or may even exacerbate (D-cycloserine; a partial agonist) (Goff et al., 1999a) psychotic symptoms in patients already receiving clozapine. This is explained by competition of these glycinergic agents with clozapine that acts as a partial agonist at glycine sites of NMDA receptors (Tsai et al., 1999), but not with typical antipsychotic drugs (Goff et al., 1999a; Leiderman et al., 1996; Potkin et al., 1999; Tsai et al., 1999). Recent studies (Evins et al., 2002; Heresco-Levy et al., 2002) have reported improved efficacy of risperidone and olanzapine following addition of D-cycloserine.

One of the limitations of this study is that the data of the amino-acid measures were from subjects who were withdrawn from medications for a relatively short period. The ability of typical neuroleptics to decrease plasma levels of serine (Waziri and Mott, 1986) and glycine (Baruah et al., 1993) has been reported, although it may not be conclusive (Rao et al., 1990). As discussed above, the results of this study are consistent with the ability of neuroleptics to decrease serine but not glycine levels. Also, a study with a small number of subjects with schizophrenia receiving clozapine has shown no effect of this drug on plasma glycine levels (Evins et al., 1997). Clearly, there is need for further study to investigate the effect of antipsychotic drugs, including clozapine, on plasma glycine and serine levels, as well as their ratio, which would help clarify the importance of these amino-acid measures to the pathophysiology of schizophrenia.

In conclusion, the results of this study indicate that plasma glycine levels and glycine/serine ratios are decreased in schizophrenia while serine levels are increased. These results suggest that the decreased availability of glycine may be related to the aetiology of negative symptoms, and provide further support for treatment strategies involving agonists at the glycine site of the NMDA receptor, as well as for other means of enhancing NMDA receptor-mediated function.

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Statement of Interest

None.

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