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ScienceDirect
Schizophrenia Research 95 (2007) 174–178
SCHIZOPHRENIA RESEARCH
www.elsevier.com/locate/schres

# Decreased levels of plasma glutamate in patients with first-episode schizophrenia and bipolar disorder

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Received 30 November 2006; received in revised form 12 June 2007; accepted 14 June 2007
Available online 13 July 2007

**Abstract**

A variety of studies have suggested that glutamatergic neurotransmission is altered in schizophrenia and bipolar disorder. Here, we tested if plasma glutamate levels are altered in 56 patients diagnosed with schizophrenia, bipolar disorder or non-specified psychosis at the first psychotic episode and at various stages during one-year follow-up. A decrease in the levels of plasma glutamate was observed in all groups of patients at the first psychotic episode. Furthermore, plasma glutamate levels were restored after treatment in all instances. Decreased plasma glutamate levels at first psychotic episodes may reflect impaired glutamate signaling during the initial stages of schizophrenia and bipolar disorder.


*Keywords:* Glutamate; First psychotic episode; Schizophrenia; Bipolar disorder

## 1. Introduction

Glutamate is the major excitatory neurotransmitter in the mammalian brain and its effects are mediated by glutamate-gated ion channels and seven transmembrane, G-protein coupled glutamate receptors. In turn, glutamate homeostasis is driven by glutamate transporters which regulate the extracellular levels of glutamate (Danbolt, 2001). The first evidence of decreased glutamate levels in schizophrenia was reported over 25 years ago (Kim et al., 1980). Since then, mounting evidence has accumulated indicating that the dysfunction of glutamatergic neurotransmission may play an important role in the pathophysiology of schizophrenia and bipolar disorder (Tsai and Coyle, 2002; Schiffer, 2002). In particular, the hypofunction of *N*-methyl-D-aspartate (NMDA) type glutamate receptors is considered to be a key factor in schizophrenia (Olney and Farber, 1995). Thus, the psychotomimetic drug phencyclidine blocks the NMDA receptor channel (Javitt and Zukin, 1991); mice expressing low levels of the NMDAR1 subunit display behaviors which are related to schizophrenia and are ameliorated by antipsychotic treatment (Mohn et al., 1999); and treatment with positive modulators of NMDA receptors induces therapeutic benefit (Konradi and Heckers, 2003). In addition, glutamate transporter expression and function is altered in areas of the brain which are vulnerable to schizophrenia and bipolar disease (McCullumsmith and Meador-Woodruff, 2002; Matute et al., 2005). Overall, these findings suggest that glutamate signaling is impaired in schizophrenia.

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doi:10.1016/j.schres.2007.06.012

The levels of glutamate in blood plasma may reflect the extracellular concentration of glutamate within the CNS, since brain-to-blood efflux of this amino acid occurs through the blood–brain-barrier (Berl et al., 1961; O'Kane et al., 1999), but the entry from blood into the brain is minimal (Hawkins et al., 2006). Thus, although blood cells and peripheral organs may constitute the primary source of plasma glutamate, exit of glutamate from the CNS also contributes substantially to the overall concentration of glutamate in plasma, as shown in certain pathological conditions (Mallolas et al., 2006). Furthermore, atypical antipsychotic drugs increase extracellular concentrations of glutamate by reducing the expression and function of glutamate transporters (Vallejo-Illarramendi et al., 2005), and as a consequence these drugs may increase plasma glutamate levels. Indeed, several studies have reported an increased concentration of glutamate in the plasma/serum of patients with schizophrenia who had been treated with antipsychotics (Evins et al., 1997; Tortorella et al., 2001; Goff et al., 2002; van der Heijden et al., 2004). In addition, plasma glutamate levels are higher in treated bipolar disorder patients than in healthy controls (Hoekstra et al., 2006). In the present study, we set out to characterize the levels of plasma glutamate in patients with schizophrenia or bipolar disorder upon the first psychotic episode and at various intervals thereafter. We observed that the concentration of glutamate in plasma is reduced at the onset of disease in both instances but is restored to near normal levels following 1 year treatment.

## 2. Methods

### 2.1. Patients

In this study, we examined 56 patients (mean age±S.E.M., 23.3±0.94 years) from the health catchment area of Vitoria (300.000 inhabitants) (Álava, Spain), who experienced a first psychotic episode during the period 2002–2005. First psychotic episode was defined as the first time a patient displayed positive psychotic symptoms of delusions or hallucinations. This sample of patients consisting of all first-episode patients who required hospitalization and gave informed consent to participate in the study, represented 75% of the total population of patients who had been admitted to the psychiatric emergency care unit. Dropout from the study was around 40% after and occurred principally towards the end of the year of treatment. No significant differences in age, gender, or clinical symptoms were detected between included and excluded patients. 28.4% of the sample were female. Total PANSS scores (mean± S.D.) were 80.98±16.39 at baseline, 57.51±19.57 at one month, 53.33±19.04 at six months, and 51.76±16.69 at twelve months. GAF was 30.72 at baseline, 51.28 at one month, 56.19±15.26 at six months, and 56.60±14.47 at twelve months. Patients were diagnosed after 12 months of inclusion using the Structured Clinical Interview for DSM IV, SCID-I. 24 patients were diagnosed with schizophrenia, 17 with bipolar disorder, and the remaining 15 with non-specified psychotic disorders. Patients with schizophrenia had the following demographic characteristics: mean age (±S.E.M), 23.21±1.33 years; % female, 16.7%; % with at least primary level education (>eleven years of schooling), 90% and % with medium or higher socioeconomic status, 50%. Patients with bipolar disorder had the following demographic characteristics: mean age (±S.E.M), 25.29±1.71 years; % female, 35.3%; % with at least primary level education (>eleven years of schooling), 93.3% and % with medium or higher socioeconomic status, 76.9%. Patients with other psychotic disorders had the following demographic characteristics: mean age (±S.E.M), 23.36±2.59 years; % female, 40%; % with at least primary level education (>eleven years of schooling), 92.3% and % with medium or higher socioeconomic status, 69.2%. Each patient was paired by age and sex with a control subject. Patients were treated after the first episode with atypical antipsychotics (62–68%), with lithium or other mood stabilizers together with atypical antipsychotics (23–26%), with typical antipsychotics (7–11%), or received no treatment (2–4%). Ranges in each treatment group indicate changes in the drugs administered initially at the onset of symptoms and during the first year of illness.

### 2.2. Control subjects

In addition, 50 healthy volunteers were selected explicitly for the research and matched pairwise for sex and age (25.19±0.95 years, mean age±S.E.M.). Twenty one of these controls were used for comparisons with patients with schizophrenia, 15 for comparisons with bipolar disorder and 14 for comparisons with non-specified psychoses. All subjects (case and controls) were recruited from the same community and included after informed consent to participate in the study was obtained. Subjects with mental retardation, organic brain disorders, or drug abuse as a primary diagnosis were excluded. As for the patients, 44% were smokers, 52% consumed alcohol, 13% abused alcohol and 34% abused cannabis. We did not observe differences in the plasma glutamate concentration among these groups, or in comparison to the remaining patients. The exclusion criteria for controls consisted of the