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# Glutamate in Schizophrenics and Healthy Controls

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**Summary.** Cerebrospinal fluid (CSF) glutamate levels were measured in 28 paranoid schizophrenic patients and 15 healthy individuals. From the 28 patients 15 were treated with neuroleptic drugs and 13 did not take any drugs. No significant difference was found between glutamate in patients without neuroleptics and controls. However, CSF glutamate was significantly higher in patients taking neuroleptics than in controls ($P < 0.001$) or in patients without neuroleptics ($P < 0.01$).

This and other data from the literature indicate that enhanced levels of cerebral glutamate may be significant for the antipsychotic efficacy of neuroleptic drugs.

**Key words:** Schizophrenia – CSF – Glutamate – Neuroleptic drugs

**Zusammenfassung.** Bei 28 paranoid Schizophrenen und 15 psychisch gesunden Kontrollen wurde die Glutamatkonzentration im Liquor cerebrospinalis gemessen. Fünfzehn der 28 Patienten standen unter neuroleptischer Therapie, 13 waren völlig ohne Medikamente. Es ergab sich kein signifikanter Unterschied zwischen Patienten ohne Neuroleptika und Kontrollen. Allerdings war die Glutamatkonzentration bei Patienten, die Neuroleptika erhielten, signifikant höher als bei Patienten ohne Neuroleptika ($P < 0.01$) oder Kontrollen ($P < 0.001$).

Dieses Ergebnis, zusammen mit anderen Befunden aus der Literatur, läßt daran denken, daß die Steigerung der cerebralen Glutamatkonzentration nicht ohne Bedeutung für die antipsychotische Wirksamkeit der Neuroleptika sein mag.

## Introduction

Glutamate is an amino-dicarboxylic acid present in the central nervous system (CNS) of mammals and other species with the highest concentration in the nucleus

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accumbens, cerebral cortex and cerebellum (Costa et al. 1979). It functions as a detoxifying substrate trapping ammonia to form glutamine, and further as the precursor of $\gamma$-amino butyric acid (GABA). Moreover, certain biochemical and pharmacological characteristics have suggested that this substance may be a serious candidate for the role of a neurotransmitter (Johnson 1972). There is experimental evidence that glutamatergic neurons exist in corticostriatal and hippocamposeptal tracts of the CNS (Cotman et al 1981).

In a recent report, Kim et al. (1980) investigated cerebrospinal fluid (CSF) glutamate in 20 schizophrenic patients and 44 controls and found that CSF glutamate in the patient group was decreased to approximately half that of the control value ($13.4 \pm 0.6$ nmol/ml in patients versus $25.8 \pm 0.7$ in controls). Although in this study most of the patients were taking neuroleptic drugs ($n = 16$), it was hypothesized that neuroleptic drugs should increase rather than decrease glutamate in the brain.

In order to reexamine these findings and to explore this hypothesis further, we carried out the present investigation.

## Material and Methods

Twenty-eight paranoid patients from the Clinica Borda do Campo, Brazil, (all males, mean age $30.6 \pm 8.0$ years) and 15 control subjects (13 males and 2 females, mean age $35.9 \pm 15{,}8$ years) were selected for the study. Patients were diagnosed according to the Research Diagnostic Criteria (Spitzer et al. 1975). Two experienced psychiatrists independently evaluated the psychopathological state of the patients by means of the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962). Fifteen patients were under treatment with neuroleptic drugs (butyrophenones and phenothiazines) and 13 patients were drug free for a period of at least four weeks prior to the study. Further data from the patient group are noted in Table 1. The psychopathological ratings on the BPRS are summarized in Table 2.

Controls were subjects with nonspecific neurological symptomatology (headaches, dizziness etc.) which necessitated a lumbar puncture for diagnostic reasons. Informed consent was obtained from all of the subjects of their first degree relatives after the nature of the study and possible complications had been fully explained.

CSF was obtained by lumbar puncture in sitting position between 9 and 10 a.m., after probands had fasted for 12 h and had bed rest for 10 h. Samples were immediately frozen on dry ice and then stored frozen at $-50°$ C. When the clinical work was concluded, samples were transported from Brazil to Germany in a container with dry ice and then stored at $-70°$ C until the assays were performed (within 2 weeks). Glutamate and glutamine were determined by the fluorometric method (Graham and Aprison 1966), the origin of each sample being unknown to the examiner.

**Table 1.** Separation of the patients into those receiving neuroleptic treatment and those without treatment and their age, duration of illness and number of hospitalizations

| | Patients with neuroleptics ($N = 15$) | Patients without neuroleptics ($N = 13$) | All patients ($N = 28$) |
|---|---|---|---|
| Age (years) | $31.8 \pm 10.2$[a] | $29.3 \pm 4.4$ | $30.6 \pm 8.0$ |
| Duration of the disease (years) | $10.8 \pm 6.8$ | $8.2 \pm 4.5$ | $9.0 \pm 6.3$ |
| Number of hospitalizations | $13.6 \pm 10.0$ | $7.5 \pm 7.3$ | $11.5 \pm 9.4$ |

[a] $\pm$ standard deviation

**Table 2.** Scores of the Brief Psychiatric Rating Scale (BPRS) for the groups of patients receiving neuroleptics, without neuroleptics and for the patient group as a whole. *Score 1:* Anxiety-depression. *Score 2:* Anergia. *Score 3:* Thought disturbance. *Score 4:* Activation. *Score 5:* Hostile-suspiciousness. *Score 6:* Total score

| BPRS | Patients with neuroleptics ($N=15$) | Patients without neuroleptics ($N=13$) | All patients ($N=28$) |
|---|---|---|---|
| Score 1 (ANDP) | 7.0± 4.5[a] | 5.3±1.7 | 6.2± 3.5 |
| Score 2 (ANER) | 12.9± 4.6 | 14.5±4.8 | 13.4± 4.3 |
| Score 3 (THOT) | 14.5± 7.6 | 15.6±5.7 | 15.0± 6.7 |
| Score 4 (ACTV) | 3.8± 1.8 | 6.4±3.1 | 5.0± 2.8 |
| Score 5 (HOST) | 6.4± 4.3 | 8.5±4.7 | 7.4± 4.6 |
| Score 6 (TOTAL) | 44.6±11.4 | 49.7±9.0 | 46.9±10.5 |

[a] ± standard deviation

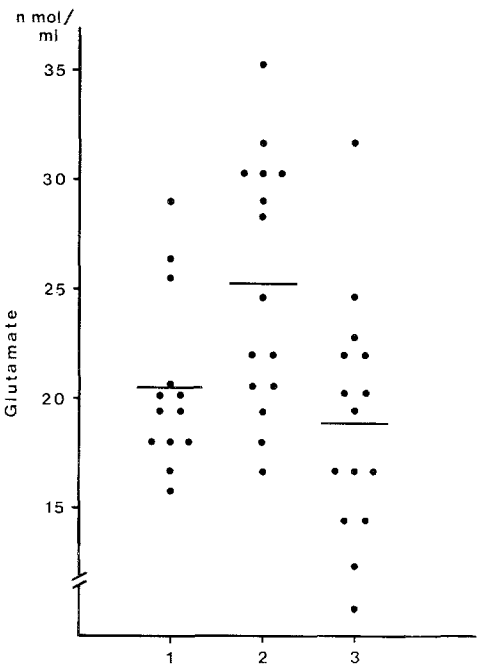


**Fig. 1.** Levels of glutamate in cerebrospinal fluid in 1. patients without neuroleptic drugs ($N=13$); 2. patients with neuroleptic drugs ($N=15$) and 3. healthy controls ($N=15$)

## Results

Results of glutamate estimations are summarized in Fig. 1. Levels of CSF glutamate were significantly higher in the group of patients taking neuroleptic drugs (25.25±5.76 nmol/ml) than in controls (18.86±5.57 nmol/ml) or in drug free patients (20.55±3.98 nmol/ml; $P<0.001$ and $P<0.01$, respectively). No significant difference was found in CSF glutamate between patients not taking neuroleptics and controls.

In the group of patients as well as in the controls, CSF glutamate did not correlate with age. In the patient group no significant correlation appeared between CSF glutamate levels and duration of illness, number of psychiatric hospitalizations or psychopathological scores as measured on the BPRS.

There was no difference in CSF glutamine between schizophrenic patients and controls and it did not correlate with CSF glutamate nor with the variables considered above.

## Discussion

In spite of certain clinical and pharmacological controversies, the dopamine hypothesis of schizophrenia continues to be thought of at least as pertinent. Rowlands and Roberts (1980) found that the activation of dopamine receptors inhibits the calcium-dependent glutamate release from corticostriatal terminals. It could thus be expected that schizophrenic patients should have decreased glutamate levels in the CNS as was found by Kim et al. (1980).

However, in the present study we have failed to replicate this finding and we are unable to explain these discrepancies. Some methodological differences between the two studies could not be avoided, such as the use of different diagnostic criteria for the selection of patients, racial heterogeneity, age, sex and dietary differences. Nevertheless, the lack of correlation between the levels of CSF glutamate and psychopathological factors (BPRS) and age in our study, as well as the similarity between CSF glutamate in males and females (JS Kim, personal communication) minimizes at least in part the account of those differences for the conflicting results. Further studies in this area are needed before any conclusion can be drawn.

On the other hand, results provided here indicate that the blockade of dopamine receptors (by neuroleptic drugs) may enhance the release of glutamate and thus increase its concentration in lumbar CSF. This would be expected from laboratory observations (Rowlands and Roberts 1980).

In this context it is of interest that the release of glutamate in brain was found to increase after electrical stimulation (Bradford 1970; Hammerstadt and Cutler 1972) and that many convulsant compounds (e.g. isoniazid) inhibit glutamate decarboxylase which would be compatible with an accumulation of glutamate in the CNS.

These facts considered together suggest, but certainly do not establish, that the antischizophrenic effect of neuroleptic drugs, seizures and electroconvulsive treatment may partially be due to a commonly increased level of glutamate in brain rather than to dopamine receptor blockade alone.

Glutamic acid is widely used as a central stimulant and has been prescribed in various psychic disorders including depression and schizophrenia (Giese 1953). The mechanism by which orally administered glutamic acid may be operative is unclear, as only small amounts penetrate the blood-brain barrier (Partridge 1979) and the therapeutic results as far as psychoses are concerned remain equivocal.

Future research should determine more precisely the role of glutamic acid in psychoneurobiology.

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