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Increased Serum Glutamate in Depressed Patients

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Summary. Glutamate concentration was determined in serum from endogenous and neurotic depressive patients, in persons with schizophrenia or schizoaffective disorder, and in normal subjects.

The mean serum glutamate level in the endogenous and neurotic depressive patients was found to be significantly higher than in any of the other groups. No other statistically significant differences were found. Statistical analysis revealed that the elevated serum glutamate concentration in the endogenous and neurotic depressive patients was probably caused by medication. These results are discussed in view of the effect of antidepressants upon the serum glutamate in the affective disorders.

Key words: Serum glutamate – Endogenous depression – Neurotic depression – Antidepressants

Zusammenfassung. Der Serum-Glutamatgehalt wurde bei endogen depressiven, neurotisch depressiven, schizophrenen und schizoaffektiven Patienten sowie gesunden Kontrollpersonen bestimmt.

Hierbei zeigte sich, daß die Serumglutamatspiegel bei endogen und neurotisch Depressiven signifikant höher waren als bei den anderen Gruppen. Zwischen schizophrenen und schizoaffektiven Patienten sowie Kontrollen zeigten sich dagegen keine signifikanten Unterschiede. Die weitere Analyse der Daten erbrachte die Hypothese, daß die erhöhten Serum-Glutamat-Konzentrationen bei endogen und neurotisch Depressiven eine Folge der antidepressiven Medikation sind. Diese Ergebnisse werden im Hinblick auf die Wirkung der Antidepressiva auf das Serum-Glutamat bei affektiven Störungen diskutiert.

Schlüsselwörter: Serum-Glutamat – endogene Depression – neurotische Depression – Antidepressiva

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Introduction

For the last two decades biochemical hypotheses on the etiology of depression and mode of action of antidepressant drugs have focused on two neurotransmitters, norepinephrine and serotonin (5-hydroxytryptamine). Evidence of a deficiency of serotonin in the brain of depressives has arisen from post-mortem studies (Shaw et al. 1967; Hornykiewicz 1974; Birkmayer and Riederer 1975), and from reports of a reduction of 5-hydroxy-indolacetic acid (5-HIAA), the principal metabolite of serotonin, in CSF (Coppen et al. 1972; Mendels et al. 1972; Asberg et al. 1976), and decreased 5-HIAA accumulation in CSF after probenecid administration (Van Praag et al. 1970).

In serum, the precursor of serotonin L-tryptophan and its non-albumin bound portion free tryptophan, have also been reported to be lowered in depressives, though reports are controversial (Coppen et al. 1973; Riley and Shaw 1976; Schmid-Burgk et al. 1981). These findings led to therapeutic trials with L-tryptophan or L-5-hydroxytryptophan given orally; the results achieved however are conflicting (Angst et al. 1977; d'Elia et al. 1978). In examining the plasma ratio of tryptophan to neutral amino acids which compete with tryptophan for the same carrier system across the blood-brain barrier, Moller et al. (1980) found a decreased ratio in some of the depressive patients. They were able to show that these so-called low-ratio patients responded well to treatment with L-tryptophan. Furthermore, in their original report Moller et al. (1976) also mentioned a trend toward an increase in plasma glutamate, an amino acid which is not presumed to compete for the same transport system as tryptophan (Pardridge 1977).

Glutamate is one of the most widely distributed excitatory substances in the brain, where it may function as an important transmitter. However, the role of serum glutamate is not well known.

In the present work, in order to replicate Moller's findings and to clarify a possible role for serum glutamate, we measured glutamate in the serum of depressive patients by the enzymatic fluorometric method and extended our investigation to two other psychiatric populations i.e. schizophrenic and schizoaffective disorders. To our knowledge, this is the first study comparing serum glutamate between psychiatric patients in four major diagnostic groups and normal control subjects.

Patients and Methods

Subjects were psychiatric patients residing at two different psychiatric hospitals[1]. Diagnostic classification was based on the data of standard psychiatric interviews and case histories, requiring agreement of at least two psychiatrists. Diagnoses were made according to the International Classification of Diseases (ICD-9). All depressive patients (except 8 of the endogenous depressive group and 9 of the neurotic group) received different tricyclic and tetracyclic antidepressants. All psychotropic drugs were withdrawn 3 to 6 days before sample collection; in schizophrenic and schizoaffective patients neuroleptic medication was continued. Controls were 34 volunteers without any history of psychiatric illness, recruited from medical personel. All patients and controls had normal physical activity and received an ordinary

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Table 1. Patient material

Disorder	Number and sex of patients	Mean age (years) ± SEM	Range
Control	34 (20 M, 14 F)	41.0 ± 17.2	18 - 83
Neurotic depression	27 (11 M, 16 F)	44.5 ± 10.4	29 - 66
Endogenous depression	37 (15 M, 22 F)	51.8 ± 13.0	20 - 72
Schizophrenia	20 (5 M, 15 F)	39.6 ± 16.0	17 - 79
Schizoaffective disorder	9 (0 M, 9 F)	53.0 ± 14.1	21 - 72

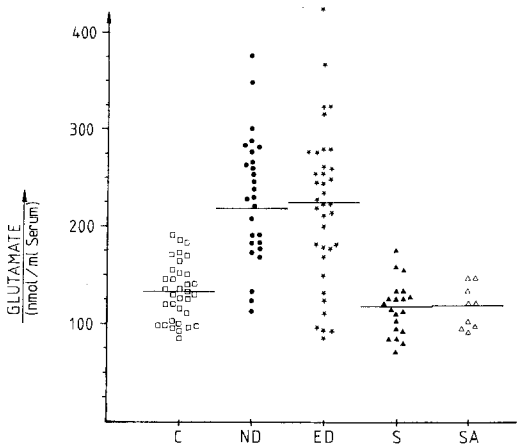

Fig. 1. Glutamate concentration in serum of control subjects *(C)*, neurotic depressive patients *(ND)*, endogenous depressive patients *(ED)*, schizophrenic patients *(S)* and schizoaffective patients *(SA)*. Horizontal lines represent arithmetic means

mixed diet. Table 1 gives further characteristics of the subjects. Blood samples were collected between 8:00 and 9:00 a.m., with patients and controls fasting overnight. The serum was separated by centrifugation and immediately frozen at −60° C with dry ice, and then stored in a deep freeze at −80° C until analysis. The serum glutamate was measured by the enzymatic fluorometric method of Graham and Aprison (1966). The method is based on the measurement of NADH formed as glutamate is converted to L-ketoglutarate by glutamate dehydrogenase. The fluorescence was read on an Aminco-Bowman SPF-500 spectrophotofluorometer. All samples were assayed in triplicate.

Most of the endogenous and neurotic depressive patients constituted part of a patient sample where free tryptophan and total tryptophan had been measured previously; those results have been reported elsewhere (Schmid-Burgk et al. 1981).

Results

Our results show a significant increase in serum glutamate in depressive patients regardless of their classification as compared to controls, schizophrenic and schizoaffective patients (Fig. 1, $P<0.001$). The level is not significantly different between schizophrenic, schizoaffective patients and controls. When dividing both depressive groups into patients who were treated with antidepressants before sample collection and those who were not (Table 2), it can be seen that only patients under treatment until 3 days prior to sample collection show a sig-

Table 2. Serum glutamate levels in endogenous depressive and neurotic depressive patients with and without treatment

Disorder	Number of patients	Mean glutamate (nmol/ml±SEM)
Endogenous depression		
Total	37	214.4±23.3
Treated	29	235.0±26.9
Untreated	8	132.4±16.5
Neurotic depression		
Total	27	220.5±27.2
Treated	18	254.0±33.8
Untreated	9	165.0±28.0

Table 3. Increase in serum glutamate levels of 4 depressive patients treated with antidepressants

Patient	Glutamate (nmol/ml)	
	Before	After
No. 1	157.5	323.8
No. 2	138.3	236.3
No. 3	164.5	257.3
No. 4	117.3	259.0

nificant increase in glutamate ($P<0.001$). In contrast, untreated patients show normal values as compared to controls. In 4 depressive patients, we measured a clear increase in serum glutamate following antidepressant treatment (Table 3). No difference in the glutamate levels of neurotic and endogenous depressives could be demonstrated, whether treated or not (Table 2). There was no correlation between glutamate level and age. Furthermore, we found no correlation between the previously reported values of total tryptophan and glutamate in either endogenous depressive or neurotic depressive patients. The same applies to the correlation between free tryptophan and glutamate in both groups. In addition, neither the ratio of total tryptophan vs. glutamate nor the ratio of free tryptophan vs. glutamate yielded a difference between both groups, whether treated or not. Thus we have no argument in favor of a competing role for glutamate for the transport system of tryptophan across the blood-brain barrier.

Discussion

The increase of glutamate in the serum of treated depressive patients may be explained by several possibilities.

i) The increase represents an effect of the antidepressant treatment which persists for 3 to 6 days after drug withdrawal. Though all of our patients had been without drugs for at least 3 days, this conclusion seems to us the most likely.

Untreated patients show the same serum glutamate levels as controls, schizophrenic and schizoaffective patients. Furthermore, there was an evident increase in serum glutamate in four depressive patients after 2 months of treatment with antidepressants. In addition, as we shall report, chronic administration of amitriptyline to rats led to an increase in serum glutamate levels.

ii) Another possible explanation might be that the increase in glutamate represents a parallel to the finding of the decreased ratio of tryptophan to competing neutral amino acids (Moller et al. 1980) and may thus have a similar significance in depression. However, glutamate has not been reported to compete with tryptophan for transport across the blood-brain barrier and thus appears less likely to influence serotonin metabolism in the brain. Moreover, we found no relationship between total tryptophan or free tryptophan and glutamate.

iii) That the increase in serum glutamate might reflect an increase of glutamate in the CSF is very unlikely for the following reasons: (a) Glutamate passes the blood-brain barrier very poorly. (b) As we shall report, the administration of antidepressants induced no change in CSF glutamate. (c) The CSF glutamate level is much lower than the serum concentration.

An influence of diet cannot be completely ruled out though all psychiatric patients in our study received the same ordinary hospital food. For the reasons mentioned above, we consider the first explanation for the increase in serum glutamate to be the most likely.

Though our patients had been free of drugs for at least 3 days, the increase in serum glutamate indicates a persisting drug effect. Therefore a drug-free period of 3 days must be considered too short. We do not know how antidepressants cause this phenomenon, but we are certainly dealing here with a peripheral effect. Serum glutamate is determined mainly by dietary intake and transport and metabolism in gut and liver (Stegink et al. 1979). But the level of corticosteroids and the functioning of the thyroid gland also influence the serum glutamate (Munro 1979) and thus represent possible mechanisms for antidepressants causing an increase in glutamate. More work seems to be necessary to clarify this phenomenon and the role of glutamate in depression.

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