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Relationships between clinical effects and monoamine metabolites and amino acids in sulpiride-treated schizophrenic patients

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Abstract. Twenty-four acutely ill schizophrenic patients (DSM–III–R), 18–42 years old, were treated for 6 weeks with sulpiride. Sulpiride was administered in three different daily dosages (400, 800 or 1200 mg) according to a double dummy blind randomized administration schedule. The psychopathology of the patients was rated by the Comprehensive Psychopathological Rating Scale (CPRS) and the Nurse's Observation Scale for Inpatient Evaluation (NOSIE). The monoamine metabolites homovanillic acid (HVA), 5-hydroxy-indoleacetic acid (5-HIAA), 4-hydroxy-3-methoxy-phenylglycol (HMPG) and the amino acids tyrosine, tryptophan, glutamate and glutamine were measured in serum before and once a week during sulpiride treatment. There were no significant correlations between the CPRS or the NOSIE morbidity scores and the biochemical measures before drug treatment. HVA levels were not correlated to rating scores during treatment, but after 6 weeks HVA had decreased significantly in the patients with a good response but not in the patients with a poor response. A negative relationship between 5-HIAA levels and depressive and negative symptoms was found. Non-responders according to the subscale for depression had low 5-HIAA levels throughout the treatment. An increase of tryptophan was correlated to improvement in the early part of treatment. High levels of glutamate or glutamine were found in non-responders before treatment. During treatment an increase of the glutamate level was correlated to improvement. Low levels of glutamine were related to improvement according to global and NOSIE (total) rating scores. Peripheral biochemical measures may be a valuable tool in the study of pathophysiological mechanisms and treatment effects in patients with schizophrenia.

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Key words: Sulpiride – Schizophrenia – Serum – Monoamine metabolites – Amino acids

Neuroleptic drugs are considered to mediate their antipsychotic effect through a blockade of central dopamine (DA) receptors. The immediate result of the receptor blockade is an increased DA turnover which can be demonstrated in man by measuring levels of the DA metabolite homovanillic acid (HVA) in cerebrospinal fluid (CSF) (Sedvall et al. 1975). Relationships between an increase of HVA in CSF and a decrease of psychotic symptoms in the early phase of neuroleptic treatment of schizophrenic patients have also been found (Wode-Helgodt et al. 1977; Alfredsson et al. 1984). However, studies of relationships between changes in DA metabolism and schizophrenia are complicated by difficulties in performing repeated lumbar punctures of the patients. During the last few years several studies have been published where HVA levels in plasma have been measured and related to the outcome of neuroleptic therapy (Harris et al. 1984; Pickar et al. 1984; Bowers et al. 1986; Chang et al. 1988; Davila et al. 1988). It is believed that about 30–50% of plasma HVA is derived from the brain (Kopin 1978; Maas et al. 1980). The results from the plasma studies are not unequivocal; Harris et al. (1984) did not find any correlation between plasma HVA levels and clinical response. Bowers et al. (1984) reported that changes in HVA levels after neuroleptic treatment differed between good and poor responders. This finding was replicated by Chang et al. (1988), who found that patients with a good outcome had a significant decline of plasma HVA over time, while poor responders had a significant increase of HVA in the early period of haloperidol treatment.

The other two monoaminergic transmitter systems – the noradrenergic and the serotoninergic – have also been implicated in the pathophysiology and treatment of schizophrenia. There is a high positive correlation between 4-hydroxy-3-methoxyphenylglycol (HMPG) levels in plasma and CSF (Kopin et al. 1983). In several studies increased levels of the noradrenaline (NA) metabolite HMPG have been found in both CSF and plasma from untreated schizophrenic patients (Härnryd et al. 1984; Bjerkenstedt et al. 1985; Bowers et al. 1986; Ko et al. 1988). During drug treatment the HMPG levels were normalized. This may indicate that serum HMPG could be used to follow treatment effects. In patients with schizophrenia within the family increased CSF levels of 5-hydroxy-indoleacetic acid (5-HIAA) have been found (Sedvall and Wode-Helgodt 1980). According to our knowledge, the usefulness of measuring 5-HIAA in serum for clinical evaluation of treatment is not known.

Some of the amino acids are precursors to the monoamines or are themselves transmitters in the brain, which make them of interest in neuropsychiatric disorders. Aberrant levels of amino acids have also been found in body fluids of schizophrenic patients. Some of the amino acids of the L-system were found in higher concentrations in plasma from schizophrenic patients than in healthy volunteers (Bjerkenstedt et al. 1985). The elevated amino acids will compete with the transport of tyrosine into the brain, and a decrease in tyrosine transport was suggested to explain the low CSF levels of HVA found in the patients. In fact, a study with positron emission tomography indicates that the influx of tyrosine from plasma to the brain may be lower in patients with schizophrenia (Wiesel et al. 1989b). Tryptophan levels in plasma will influence the synthesis of serotonin in the brain and thereby 5-HIAA levels (Fernström and Wurtman 1971). Tryptophan levels and a decreased serotonin turnover have been related to depressive symptoms (Åsberg et al. 1976; Möller 1985) and, as cited above, increased 5-HIAA levels in CSF have been found in schizophrenic patients (Sedvall and Wode-Helgodt 1980). The amino acid glutamate, an excitatory transmitter in CNS (cf Fonnum 1984), interacts reciprocally with DA in the striatum (Roberts et al. 1982; Cheramy et al. 1986). There is also a glutamate hypothesis in schizophrenia, which states that there is a hypofunction of central glutamatergic neurons in schizophrenia (Kornhuber et al. 1984). It would be of interest to find out if glutamate in serum is changed during neuroleptic treatment, which may reflect an interaction between glutamate and dopamine. Glutamine was also determined, since it is both the end product and the precursor to glutamate (Munro 1979).

The reported findings encouraged us to analyse the monoamine metabolites and the amino acids in plasma or serum from schizophrenic patients before and during neuroleptic treatment. In contrast to previous studies, we analysed all the substances in the same patients, making it possible to study relationships among several biochemical measures and the clinical outcome. In a dose-response study of sulpiride in schizophrenic patients, serum samples were collected for the determination of the monoamine metabolites and their precursor amino acids tyrosine and tryptophan. Glutamate and its precursor glutamine were also determined. In a previous paper (Alfredsson and Wiesel 1989) we described the effect of sulpiride treatment on the levels of the monoamine metabolites and amino acids in serum. The most consistent finding was a reduction of HMPG that persisted during the whole period of treatment. There was also a significant reduction in HVA level in the latter period of treatment. In this paper relationships among the monoamine metabolites, the amino acids and the therapeutic effects of sulpiride were analysed in the same patients.

Methods

The protocol of the study was approved by the Ethics Committee of the Karolinska Hospital, Stockholm, Sweden.

Selection of subjects. Patients with an acute psychosis of the schizophrenic type were selected for the study. The DSM–III–R criteria for schizophrenia had to be fulfilled for inclusion in the study (Spitzer and Williams 1987). The patients were treated as inpatients in the psychiatric clinic, Karolinska Hospital. Patients with organic brain disorder, somatic disease, alcohol and drug abuse were excluded. A total of 26 patients consented to participate after having been informed about the purpose of the study. However, two patients were excluded, since it was found that they did not fulfill the inclusion criteria. Fourteen of the remaining patients were men and 10 were women. The age range was 18–42 years. Physical examination and routine blood and urine tests indicated that all the patients were physically healthy. According to anamnestic information obtained from the patient and relatives, seven of the patients had never received neuroleptic treatment. Four patients had been off oral neuroleptics for at least 2 weeks and the remaining patients for at least 1 month before the study was started. Depot neuroleptics had not been given during the last 6 months.

Drug administration. Sulpiride (Dogmatil 200 mg, Essex Läkemedel, Sweden) was administered in a dose of 400, 800 or 1200 mg/day for 6 weeks according to a double dummy blind randomized procedure. The dose of sulpiride was divided into two equal parts and was administered at 8 a.m. and 8 p.m., respectively. After 3 weeks' treatment the design of the study involved an increase of the dose from 400 to 800 mg/day or from 800 to 1200 mg/day, or a decrease of the dose from 1200 to 800 mg/day or 800 to 400 mg/day, respectively and the patients were treated for another 3 weeks (Wiesel et al. 1989a).

Sampling of serum. All patients had fasted for 12 h before the blood sampling at 8.00 a.m. The samples were collected by venipuncture and centrifuged within 30 min at 2000 g for 15 min. The serum fractions were stored at a temperature of $-80°$ C pending analysis.

Monoamine metabolites in serum. Concentrations of HVA and 5-HIAA were determined by gas chromatography-mass spectrometry with selective ion monitoring, principally according to the method used for the metabolites in CSF (Swahn et al. 1976); for modifications for HVA in serum see Hunneman (1983) and for 5-HIAA in serum see Alfredsson et al. (1988b).

Serum levels of HMPG were analysed by gas chromatography-mass spectrometry with selective ion monitoring according to Sjöquist et al. (1975) and Swahn et al. (1976), except that 1 ml citrate buffer (pH = 6) was added to the serum sample (1 ml) in order to decrease variation during extraction.

Tryptophan and tyrosine in serum. Concentrations of tryptophan in serum were determined by HPLC fluorescence detection according to Beck and Hesselgren (1980). The same method was used for tyrosine.

Glutamate and glutamine in serum. Concentrations of glutamate and glutamine in serum were determined by high performance liquid chromatography (HPLC) fluorescence detection after derivatization with ophthaldialdehyde (Lindroth and Mopper 1979; Alfredsson et al. 1988a).

Ratings of psychopathology. By selecting individual items from the Comprehensive Psychopathological rating Scale, CPRS (Åsberg et al. 1978), different subscales were constructed (Härnryd et al. 1984) (Table 1). A subscale (CPRSΣ10) was used covering a wide range of psychotic symptoms (idem). Another subscale, CPRSΣ6, covered positive psychotic symptoms (Table 1). The CPRSΣA (autism) was constructed to reflect autistic or negative symptomatology. Depressive symptoms were rated according to the Montgomery–Åsberg scale for depression (CPRSΣDep) (Montgomery and Åsberg 1979). A high score means a pronounced psychopathology. The different items are presented in Table 1. The patient's behaviour on the ward was rated by a trained research nurse with the Nurse's Observation Scale for Inpatient Evaluation (NOSIE) (Honigfeld et al. 1966). A high total score represents an adequate behaviour. The scale consists of six subscales, three positive factors-social competence, social interest and personal neatness – and three negative factors-irritability, manifest psychosis and retardation. A high score on a negative factor means a pronounced symptomatology.

Table 1. Construction of subscules

CPRS item no.	CPRS morbidity measures				
	Global	Σ6	Σ10	ΣA	ΣDep
1. Reported sadness					x
3. Inner tension			x		x
5. Inability to feel				x	x
6. Pessimistic thoughts					x
7. Suicidal thoughts					x
13. Indecision			x		
14. Lassitude				x	x
16. Concentration difficulties			x		x
18. Reduced appetite					x
19. Reduced sleep			x		x
29. Feeling controlled		x	x		
30. Disrupted thoughts		x	x		
31. Ideas of persecution		x	x		
33. Delusional mood		x			
36. Other delusions		x			
37. Commenting voices		x[a]	x		
38. Other auditory hallucinations		x[a]			
39. Visual hallucinations		x[a]			
40. Other hallucinations		x[a]			
41. Apparent sadness					x
45. Lack of appropriate emotion			x		
49. Withdrawal				x	
54. Reduced speech				x	
57. Incoherent speech			x		
60. Slowness of movement				x	
65. Hallucinatory behaviour		x[a]			
66. Global rating of illness x					

[a] The item with the highest score was taken for the formation of the Σ6

Statistics. The product moment correlation coefficient was calculated to study relationships among biochemical measures and psychiatric rating scores. Correlations between levels of monoamine metabolites and amino acids (absolute levels and changes as compared to pretreatment levels) and rating scores (absolute levels and changes) were calculated for each point in time. Student's *t*-test was used for analysis of differences within and between groups. Two-tailed tests were used.

Results

Correlations between rating scores and biochemical measures

There were no significant correlations between monoamine metabolites or amino acids and morbidity scores before sulpiride treatment. The 5-HIAA levels showed several negative correlations to the CPRS rating scores during treatment (Table 2a, Fig. 1). Thus, patients with higher 5-HIAA levels had lower scores for autistic and depressive symptoms than patients with lower 5-HIAA levels. There were significant correlations between glutamine in serum and the global and the NOSIE total rating scores (Table 2a). Patients with lower glutamine levels were more improved. A decrease in HMPG levels was correlated with an increase in NOSIE total scores, i.e. an improvement (Table 2b). After 1 week's sulpiride treatment changes in tryptophan levels were negatively correlated to changes in scores for global morbidity, positive (Σ6) and psychotic (Σ10) symptoms (Table 2b). Patients with an increase in tryptophan showed a reduction in these morbidity scores (Fig. 2). The glutamate levels were not correlated to the rating scores, but the changes in the glutamate levels were correlated to changes in CPRS rating scores (Table 2b, Fig. 3). Thus, patients with an increase in serum glutamate were more improved than patients with a decrease in glutamate.

The pretreatment levels of glutamate and glutamine were positively and significantly correlated to changes in the CPRS rating scores after 6 weeks' treatment (Table 3). Patients who had high serum levels of these amino acids before treatment did not improve to the same extent as the patients with low pretreatment levels (Fig. 4).

Biochemical measures in responders and non-responders

The patients were divided into responders and non-responders according to the changes of the rating scores for morbidity after 6 weeks treatment. Patients with a $> 50\%$ decrease of the scores were considered as responders and otherwise as non-responders. There was no relationship between dosage of sulpiride and the outcome of the treatment (Table 4). The distribution of responders and non-responders was almost equal among the different dosage groups. The pretreatment rating scores for responders and non-responders according to

Table 2a. Correlations between monoamine metabolites and amino acids in serum and CPRS scores (global, Σ6, Σ10, ΣDep, ΣA), NOTO and NORE scores in patients with schizophrenia treated with sulpiride

	Weeks				
	0	1	3	4	6
5-HIAA	ns	ns	ns	−0.44 (Σ10)* −0.49 (ΣA)* −0.45 (ΣDep)*	−0.54 (ΣDep)**
Gln	ns	ns	ns	ns	−0.51 (NOTO)* 0.60 (GLOBAL)**

Correlations between the clinical and the biochemical variables are presented only if two or more significant correlations were found. NOTO = Nosie total scores, NORE = Nosie retardation scores, Gln = glutamine
*$P<0.05$
**$P<0.01$

b Correlations between changes in monoamine metabolites and amino acids in serum and changes in CPRS scores (global, Σ6, Σ10, ΣDep, ΣA), NOTO and NORE scores in patients with schizophrenia treated with sulpiride

	Weeks			
	1	3	4	6
HMPG	ns	−0.55 (NOTO)**	−0.57 (NOTO)**	ns
Trp	−0.49 (GLOBAL)* −0.55 (Σ6)** −0.54 (Σ10)**	ns	ns	ns
Glu	ns	−0.49 (ΣDep)*	ns	−0.54 (Σ10)* −0.47 (ΣDep)*

Changes as compared to pretreatment levels. Correlations between the clinical and the biochemical variables are presented only if two or more significant correlations were found. Trp = tryptophan, Glu = glutamate
*$P<0.05$
**$P<0.01$

the different subscales were similar, with the possible exception of the subscale for autism (Table 5).

There was no significant difference in the pretreatment level of HVA between responders and non-responders (Fig. 5a). The HVA curves for responders and non-responders were of different shapes during treatment. In the responders there was a significant decline of HVA after 6 weeks' treatment (Fig. 5a).

The shapes of the HMPG curves were similar in responders and non-responders, with a significant decline during treatment (Fig. 5b).

The 5-HIAA levels were similar in responders and non-responders before treatment. After 4 weeks' treatment there was a tendency towards a difference between the responders and the non-responders (Fig. 5c). This difference was most pronounced in the subscale for de-

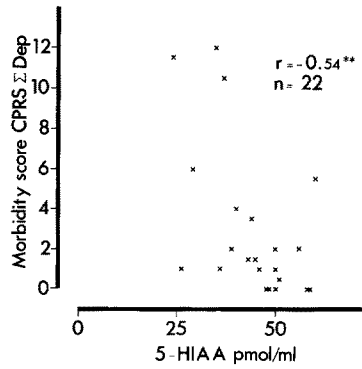

Fig. 1. The relationship between morbidity scores CPRSΣDep for depressive symptoms and 5-HIAA in serum in schizophrenic patients after 6 weeks' treatment with sulpiride. **$P<0.01$

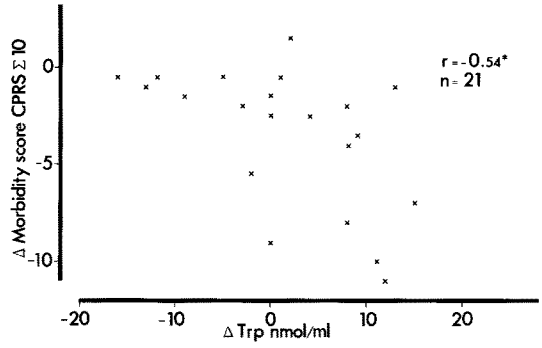

Fig. 2. The relationship between changes (Δ) in morbidity scores CPRSΣ10 for psychotic symptoms and changes in tryptophan in serum in schizophrenic patients after 1 week's treatment with sulpiride. *$P<0.05$

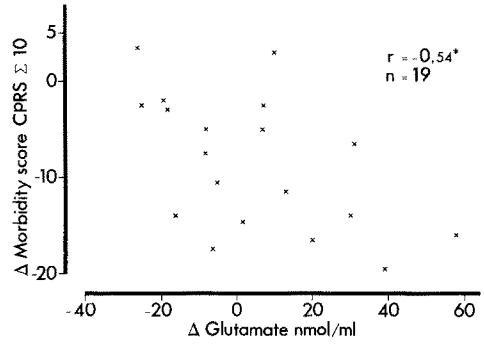

Fig. 3. The relationship between changes (Δ) in morbidity scores CPRSΣ10 for psychotic symptoms and changes in glutamate in serum in schizophrenic patients after 6 weeks' treatment with sulpiride. *$P<0.05$

Table 3. Correlations between pretreatment levels of glutamate and glutamine in serum and changes in rating scores in patients with schizophrenia treated over 6 weeks with sulpiride

	CPRS rating scores				
	Global	Σ6	Σ10	ΣA	ΣDep
Glu/ΔCPRS	ns	ns	0.52*	0.55*	0.54*
Gln/ΔCPRS	0.48*	0.48*	0.47*	0.54*	0.46*

*$P<0.05$

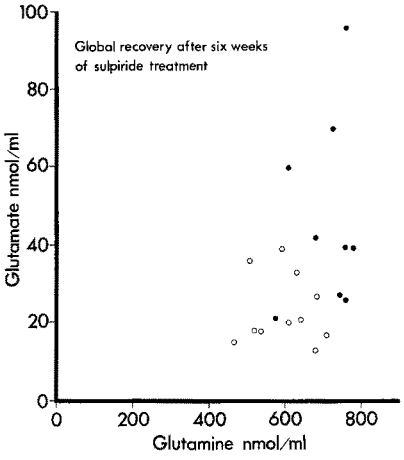

Fig. 4. Glutamate and glutamine in serum in schizophrenic patients before drug treatment. The number of patients was 20, since concentrations could not be determined before treatment in two cases and two patients dropped out after 4 weeks' treatment. ○ ≥ 50%; ● < 50%

Table 4. Number of schizophrenic patients considered as responders and non-responders in the different dose groups of sulpiride

	Sulpiride mg/day[a]			
	400–800	800–400	800–1200	1200–800
Responders[b]	4	2	1	5
Non-responders[c]	4	2	2	2

[a] The dose in the first period of treatment (0–3 weeks) followed by the dose in the last period of treatment (4–6 weeks)
[b] > 50% decrease of the global rating score after 6 weeks
[c] < 50% decrease of the global rating score after 6 weeks

Table 5. Pretreatment rating scores for schizophrenic patients who after 6 weeks' treatment with sulpiride were considered as responders or non-responders according to the different subscales for morbidity

	Rating scores				
	Global	Σ6	Σ10	ΣA	ΣDep
Responders	2.5 (12)	9.4 (14)	13.5 (15)	5.0 (11)[a]	7.7 (15)
Non-responders	2.5 (10)	9.7 (8)	13.0 (7)	2.5 (10)[b]	6.4 (7)

Mean values, figures within brackets are the number of patients
[a] One patient had a rating score of zero before treatment and was not included
[b] The difference between responders and non-responders $P < 0.1$
The number of drop-outs after 6 weeks' treatment was two

pression, in which the responders had significantly higher 5-HIAA levels during treatment than the non-responders (Fig. 5d).

Non-responders had a significant increase of tyrosine levels in serum during treatment (Fig. 6a). The tryptophan level was significantly increased after 4 weeks in the non-responders (Fig. 6b).

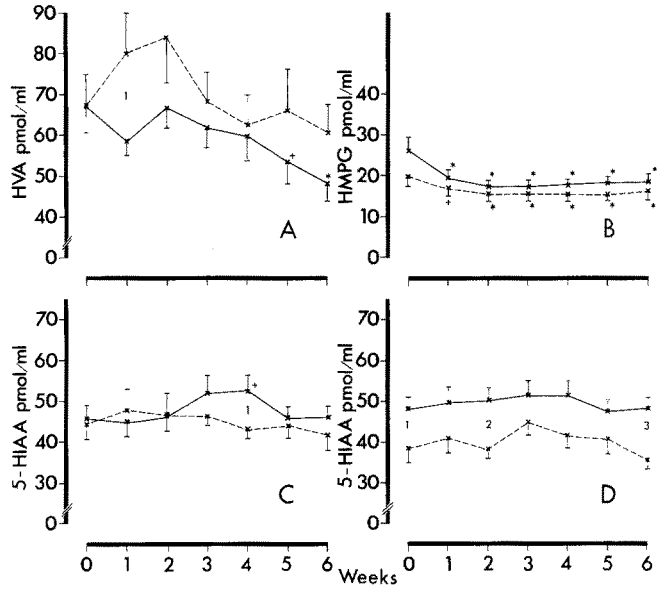

Fig. 5A–D. Serum levels of monoamine metabolites during sulpiride treatment in schizophrenic patients divided into responders and non-responders after 6 weeks' treatment. **A** HVA in serum in responders and non-responders according to the Global rating. **B** HMPG in serum in responders and non-responders according to the Global rating. **C** 5-HIAA in serum in responders and non-responders according to the Global rating. **D** 5-HIAA in serum in responders and non-responders according to the subscale for depressive symptoms. Differences as compared to pretreatment levels (Student's *t*-test for paired observations): $^{+}P < 0.1$, $^{*}P < 0.05$. Differences between responders and non-responders (Student's *t*-test for unpaired observations): $^{1}P < 0.1$, $^{2}P < 0.05$, $^{3}P < 0.01$. x——x Responders; x----x non responders

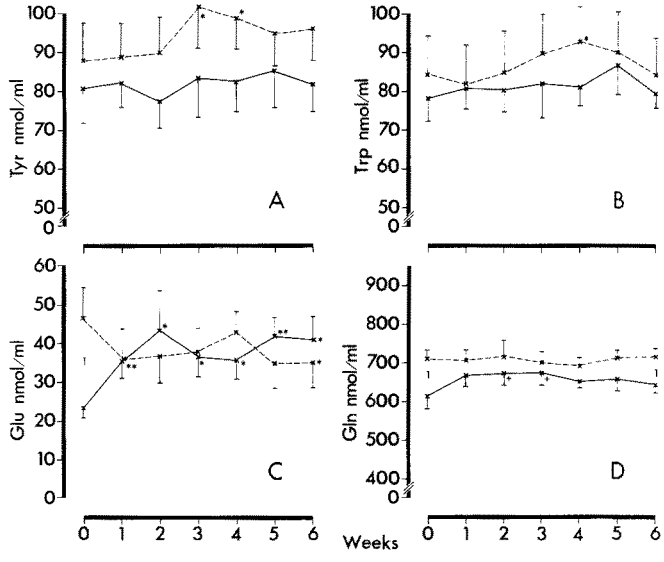

Fig. 6A–D. Serum levels of amino acids during sulpiride treatment in schizophrenic patients divided into responders and non-responders after 6 weeks' treatment according to the global rating. **A** Tyrosine in serum in responders and non-responders. **B** Tryptophan in serum in responders and non-responders. **C** Glutamate in serum in responders and non-responders. **D** Glutamine in serum in responders and non-responders. Differences as compared to pretreatment levels (Student's *t*-test for paired observations): $^{+}P < 0.1$, $^{*}P < 0.05$, $^{**}P < 0.01$. Differences between responders and non-responders (Student's *t*-test for unpaired observations): $^{1}P < 0.05$. x——x Responders; x----x non responders

The glutamate level in serum was significantly lower before treatment in the responders. During treatment the glutamate level increased in the responders, while it decreased in the non-responders (Fig. 6c). The glutamine level was lower in the responders before treatment and after 6 weeks (Fig. 6d).

Discussion

One major aim of this study was to investigate biochemical measures in serum and their usefulness as markers for disease and treatment in patients with schizophrenia. The biochemical variables measured were chosen according to hypotheses of the pathophysiology of schizophrenia and the effects of antipsychotics (for references see Introduction). The concentrations of the monoamine metabolites and the amino acids were measured in serum, which is easily accessible. However, it is uncertain how the serum fractions of the different substances represent or influence their CNS formation. On the other hand, schizophrenia involves changes not only of CNS origin; peripheral disturbances also take place (Borg et al. 1987; Hagenfeldt et al. 1987). Changes in central and peripheral cellular metabolism may very well have a similar cause, motivating the study of other compartments than the brain in patients with schizophrenia.

It has been argued that plasma should be used instead of serum for the determination of amino acids, especially when analyzing glutamate, since serum levels might be unreliable due to a contribution of intracellular glutamate from disrupted platelets and leucocytes. However, we have compared serum and plasma levels of both monoamine metabolites and amino acids and found that plasma and serum levels of all the substances were in good agreement in our preparations (Alfredsson and Wiesel 1989). Our range for serum glutamate in healthy volunteers (10–50 nmol/ml) was also within the range for glutamate in plasma (10–67 nmol/ml, Perry and Hansen 1969).

The design of the study was based on the assumption that it should be possible to find a "therapeutic window" for sulpiride treatment of psychotic patients. There was, however, a very weak relationship between the dose or the serum level of sulpiride and the therapeutic effect. Thus, responders and non-responders were almost equally distributed among the dose groups, as shown in Table 4. Since there was no relationship between the dose or the serum concentration of sulpiride and the biochemical measures (Alfredsson and Wiesel 1989), the results from the patients in the different dose groups were pooled.

HVA in plasma has previously been used to follow the effects of neuroleptic treatment (Harris et al. 1984; Pickar et al. 1984; Bowers et al. 1986; Chang et al. 1988; Davila et al. 1988). The HVA curves for responders and non-responders in this study showed the same difference as earlier was demonstrated by Chang et al. (1988), i.e. a significant decline of HVA in the responders. The fact that the patients received different doses of sulpiride did not seem to interfere with the division into responders and non-responders. If this division was made separately for patients receiving high or low doses of sulpiride, the HVA curves for the responders of both the high and the low dose groups showed a decline, which the non-responders did not. Thus, there seemed to be a difference within the patient group in how the DA system was influenced by sulpiride. This might be due to a heterogenity in the pathophysiology of schizophrenia.

A relationship between low levels of 5-HIAA in serum and autistic and depressive symptoms was found. The symptoms were not related to a decrease in 5-HIAA during treatment, but patients with low 5-HIAA levels did not improve to the same extent as the other patients. In nine of the patients lumbar puncture was also performed before treatment (to be published), and a significant negative correlation was found between 5-HIAA in CSF and depressive symptoms ($r = -0.70$; $P < 0.05$). These findings support the view of a relationship between disturbances of the 5-HT system and depression or depressive symptoms, which has been postulated for some time (Lloyd et al. 1974; Åsberg et al. 1976). This is the first time that a relationship between 5-HIAA *in serum* and depressive symptoms has been demonstrated. The observed relationship in patients with schizophrenia suggests that changes in 5-HT metabolism are coupled more to depressive symptoms than serving as a specific marker for a disease entity. The non-responders according to the score for depression tended also to have lower levels of the other monoamine metabolites, HVA (week 0 and 4, $P < 0.1$) and HMPG (week 1 and 4, $P < 0.1$) than the responders. A decreased monoamine metabolism may distinguish a subgroup of schizophrenic patients or be the extreme cases of the whole group. Sulpiride treatment did not seem to be effective in reducing the depressive symptoms in this group of patients.

The NA activity as measured by HMPG in serum was similar in good and poor responders. Serum HMPG was significantly decreased during treatment (Alfredsson and Wiesel 1989). The decline of HMPG was significantly related to improvement according to the NOSIE scale. The NOSIE scale rates behaviour in the ward rather than specific psychotic symptoms. It is therefore possible that the decrease in HMPG in schizophrenic patients after treatment was related to a general decrease in environmental stress following hospital care and adaptation to the ward.

An increase of tryptophan in the early part of treatment was correlated with improvement of global and positive symptoms. The changes in 5-HIAA in serum were significantly and positively correlated to the changes in tryptophan (Alfredsson and Wiesel 1989). The importance of the 5-HT system for the outcome of treatment was emphasized by the relationship of both the precursor amino acid (tryptophan) and the end metabolite (5-HIAA) to therapeutic effects. Serotoninergic mechanisms in schizophrenia seem worthy of further exploration.

High levels of glutamate or its precursor glutamine in serum before treatment were associated with poor outcome of treatment. Five of the non-responders had levels of glutamate or glutamine exceeding the plasma

range for healthy volunteers (Fig. 4, Perry and Hansen 1969). The shape of the time curves for glutamate also differed between responders and non-responders. The responders had significantly lower levels before treatment and a significant increase of serum glutamate during treatment. There was also a correlation between the increase of glutamate during treatment and improvement, according to two of the subscales. The correlations between the clinical ratings and the pretreatment levels and changes in glutamate in responders and non-responders may therefore indicate involvement of glutamatergic mechanisms in schizophrenia.

The responders showed a decline in HVA and an increase in glutamate during treatment. The serum levels of HVA and glutamate were negatively correlated (Alfredsson and Wiesel 1989). It may be speculated that a good response following antipsychotic treatment requires an interplay between dopaminergic and glutamatergic mechanisms. It is known that DA inhibits glutamate release in the striatum, an effect that is inhibited by DA blockers (Roberts et al. 1982; Cheramy et al. 1986). One possible interpretation of the data may be that nonresponders have a disturbance of the glutamatergic system involving the interplay between DA and glutamate neuronal mechanisms.

In conclusion, glutamate and glutamine in serum might be used to predict outcome of treatment, since patients with high levels of these amino acids before treatment improved poorly. HVA and glutamate could be used to follow the effect of treatment, since a decline of HVA and an increase of glutamate were found in the responders. Low serum levels of 5-HIAA both before and during treatment were associated with depressive symptoms. The results support the view that peripheral biochemical measures could be useful to investigate pathophysiological mechanisms and treatment effects in patients with schizophrenia.

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