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Amino acid studies in transient acute polymorphic psychosis

Review Article

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Summary. Data are reviewed on the amino acid metabolism in patients suffering from transient acute polymorphic psychoses according to ICD-10. The psychotic episodes of many of these patients are characterized by distorted sensory perceptions and intense emotional states; plasma amino acid analysis revealed a disturbed serine-glycine metabolism.

In remitted patients oral loading with serine induced the characteristic dysperceptions and psychedelic symptoms. Plasma concentrations of serine and methionine were decreased, and the concentration of taurine was increased. Fibroblast experiments suggest that the activities of the serine metabolizing enzymes serine hydroxymethyltransferase and cystathionine β-synthase are increased in these patients.

The determination of plasma amino acid concentrations proved to be useful in discriminating these patients. The prevalence of this transient psychosis in a psychiatric in-patient population ranged between 1.4 and 3.6%.

Keywords: Amino acids – Serine – TSM-ratio – Acute polymorphic psychosis

In 1980 we reported upon a group of patients suffering from psychotic episodes characterized by intense emotional states ranging from overwhelming feelings of ecstasy to terrifying anxiety (Pepplinkhuizen et al., 1980). Congruent delusions and hallucinations are fleeting in these patients, who often suffer from sensory-perceptual anomalies of the type seen after LSD ingestion (e.g. distorted perceptions of colours, objects, space, body and time).

Transient acute polymorphic psychoses

In Europe this type of psychosis has been termed bouffée délirante des degenerées (Magnan, 1893), degeneration psychosis (Schröder, 1920), atypical psychosis (Mitsuda, 1965) and later on cycloid psychosis (Perris, 1974; Leonhard, 1979), in particular the ecstasy-anxiety subform (Bruinvels and

Table 1. Transient acute polymorphic psychotic disorder with or without symptoms of schizophrenia (ICD-10)

Formerly:
bouffée délirante (des dégénerées)
cycloid psychosis (i.p. anxiety-happiness psychosis)
degeneration psychosis.
General features:
acute onset
rapid resolution of symptoms, complete recovery with no residual symptoms
mean duration: 3 months
no obvious precipitating stress
when full-blown: unstable, polymorphic, kaleidoscopic and rapidly alternating clinical picture.
Specific characteristics:
clear consciousness, except that perplexity can be present at some time
distorted perceptions of objects, space, colours, sounds, body, and time (like in LSD-induced states)
visual hallucinations (complex and simple) for the most part, besides olfactory, somatic, and auditive hallucinations
vivid visionary, cosmic, and ecstatic experiences, sometimes in a dream-like state
sudden mood swings from elated, ecstatic to terrifying anxiety and depression
perfunctory delusions of religiosity, grandeur, paranoia, and reference
psychomotor disturbances: from disinhibited manic-like behavior to erratic catatonic motor behavior and catalepsy
a period of post psychotic depersonalization can occur.

Pepplinkhuizen, 1985). ICD-10 (World Health Organization, 1992) classifies these psychoses as acute polymorphic psychotic disorders (APP) with or without symptoms of schizophrenia (F 23.0–F 23.1). A majority of the patients with APP suffer from hallucinogenic drug-like sensory anomalous perceptions (in a broadened sense psychedelic experiences or psychosensory phenomena) and these psychotic patients are designated "APP+" (Table 1). According to DSM-III-R (American Psychiatric Association, 1987), these psychotic disorders belong to the category of "Psychotic Disorders Not Elsewhere Classified", in particular to the group of schizoaffective (295.7) and schizophreniform disorders (295.40).

Generally, the disorder runs a benign course and most patients recover after a period of about three months without any residual psychopathological symptoms, though recurrence may occur. Psychological stress does not appear to evoke a psychotic episode, yet a catabolic state caused by (voluntary) fasting, surgical intervention and somatic diseases with low caloric intake could be held responsible. In line with this, a carbohydrate-rich diet with low protein and low fat contents enhanced recovery dramatically in most patients suffering from a full-blown psychosis and was preventive in many cases.

On the basis of the psychedelic characteristics it was hypothesized that – in analogy with the "transmethylation hypothesis of schizophrenia" (Osmond and Smythies, 1952) – an endogenous synthesis of hallucinogenic substances

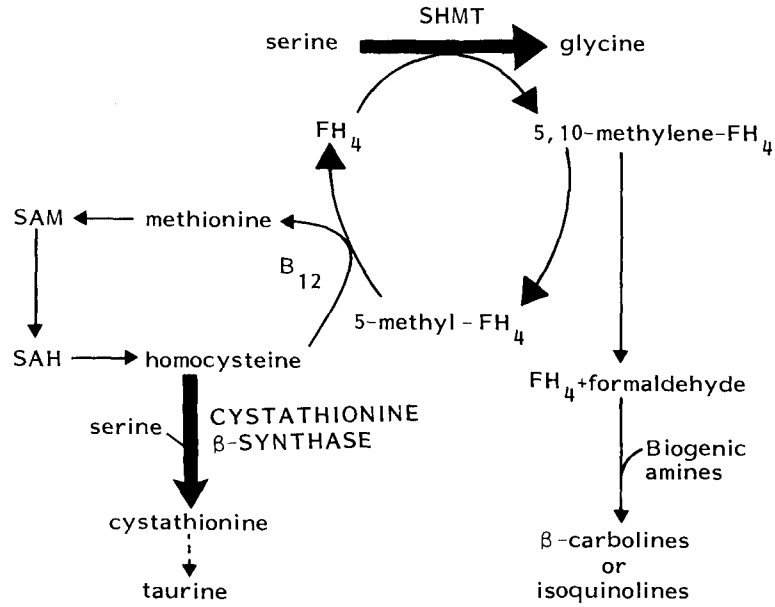

Fig. 1. Pathways involved in the metabolism of serine *SHMT* serine hydroxymethyltransferase; *FH_4* tetrahydrofolic acid; *SAH* S-adenosylhomocysteine; *SAM* S-adenosylmethionine; *B_{12}* vitamin B_{12}. Thick lines represent enzymatic steps which were found to be activated in the fibroblasts after incubation with serum obtained from patients suffering from acute polymorphic psychosis with psychosensory symptoms. Reproduced from Fekkes et al. (1991) with permission

might be responsible for the psychotic episode (Pepplinkhuizen et al., 1980). However, based on studies performed by Meller et al. (1975) and Pearson and Turner (1975) it was assumed that also in our patients not S-adenosylmethionine, but 5,10-methylene tetrahydrofolic acid could be the one-carbon moiety donor. The latter compound may accumulate in APP+ patients due to an increased conversion of serine into glycine, assuming that the capacity of the reduction of 5,10-methylene tetrahydrofolic acid into 5-methyltetrahydrofolic acid and further transport of methyl moieties is limited (see Fig. 1). An excess of 5,10-methylene tetrahydrofolic acid can easily convert into formaldehyde and tetrahydrofolic acid. Formaldehyde may react spontaneously with biogenic amines, forming isoquinolines and β-carbolines several of which are known to be potent psychotogenic substances (Brimblecombe and Pinder, 1975). Thus, a disturbed serine and related to this, folate metabolism is likely to be the cause of the synthesis of hallucinogenic agents in the APP+ patients.

Oral loading tests

The transfer of a one-carbon unit from serine to tetrahydrofolic acid in APP+ patients was stimulated by administering serine orally after complete remission of a psychotic episode; thus, the patients were free of psychiatric symp-

toms and medication. The same procedure was carried out in healthy controls and, if possible, in other patient groups as well.

The dose of serine, and of the control amino acids glycine and alanine, was fixed at 2 mmol/kg body weight. The amino acid powder, dissolved in yoghurt, was administered orally half an hour before breakfast. Blood samples were taken just before and every hour after intake of the amino acid. A total of 7 blood samples was collected.

Observations of patients and of controls were done inconspicuously, though spontaneous reports of changes in mood, perception and behaviour were encouraged and recorded, while a semi-structured interview including the typical psychopathological phenomena was carried out at the end of each loading day.

Before re-emergence of symptoms, vegetative signs, such as flushing and sweating, were observed in some patients two to three hours after intake of serine. Three patterns of psychopathology were observed during a successful evocation: a) depersonalization and behavioural inhibition, b) characteristic psychedelic symptomatology and c) psychotic symptoms, often with transition from a to b and sometimes to c. In almost all cases symptoms gradually waned after 3–8 hours and were recognized by patients as identical to their past "natural" experiences.

Most reactions were found to occur after serine intake, a few reacted to glycine and some to both serine and glycine; the percentage of APP+ patients who showed these psychopathological reactions upon loading of these amino acids was 70%. Only one patient (out of 48 APP+ patients loaded) reacted to the amino acid alanine (Pepplinkhuizen, 1983; Wunderink et al., 1986; Bruinvels et al., 1988). In this review only those patients are included in which plasma amino acid concentrations were measured. The induction of (pre)psychotic symptoms in recovered (i.e. non-symptomatic) patients is highly specific for the polymorphic psychosis with psychedelic symptoms since in polymorphic psychosis without these symptoms (APP−) and in other psy-

Table 2. Characteristics of patients and healthy controls[1]

Diagnostic category	Sex female/male	Challenge test[2]	Psychopathological reaction
APP, dysperceptions present (APP+)	16/12	18	18
APP, no dysperceptions present (APP−)	12/8	10	0
Atypical psychosis	9/3	3	0
Bipolar affective disorder	8/8	9	0
Schizophrenia	6/12	6	0
Healthy controls	10/12	15	0

[1] Reproduced from Fekkes et al. (1994) with permission.
[2] The challenge test was performed by giving the subjects an oral dose of serine (2 mmol/kg body weight) double blind compared with an equal dose of glycine and alanine. *APP*, acute polymorphic psychosis.

chiatric disorders as well as controls, psychopathological reactions to serine challenge were absent (Table 2).

Thus, a disturbed serine metabolism was assumed to be the cause of the psychotic episodes, because oral loading with serine induced the re-emergence of characteristic symptoms in most recovered APP+ patients (Pepplinkhuizen et al., 1980; Bruinvels et al., 1988). Moreover, the plasma concentrations of serine were decreased in these patients (Bruinvels and Pepplinkhuizen, 1984), suggesting an increased breakdown.

Discriminating this special group is warranted, as these patients did not respond to standard neuroleptic treatment (Bruinvels and Pepplinkhuizen, 1985), but did benefit from treatment with the serotonin$_2$ receptor blocker ritanserin (Pepplinkhuizen, 1988). LSD, mescaline and many other hallucinogenic drugs are agonists of the serotonin$_2$ receptor. It was presumed that endogenous hallucinogenic substances will act in the same way. The beneficial effect of the serotonin$_2$ receptor antagonist ritanserin is in line with this presumption.

Plasma amino acids as biological markers for APP+

It was investigated whether plasma amino acid concentrations could be used to discriminate APP+ patients. Levels of amino acids in the plasma of APP+ patients were compared with those in psychiatric patients with other types of psychotic symptomatology and a healthy control group (Fekkes et al., 1994). We evaluated 22 healthy controls (12 men and 10 women; aged 21 to 48 years) and 93 patients (47 men and 46 women; aged 19 to 53 years) who were admitted for an acute psychotic episode (see Table 3). From these patients

Table 3. Plasma amino acid levels and TSM-ratios of control subjects and psychotic patients[1]

Diagnostic category	n	Serine (μmol/l)	Taurine (μmol/l)	Methionine (μmol/l)	TSM-ratio
APP+	28	102 ± 16[2,3,4,5]	108 ± 37	23 ± 5[4]	4.80 ± 1.49[2,3,4,5]
APP−	20	115 ± 16	92 ± 35	24 ± 5	3.39 ± 1.02
Atypical psychoses	12	125 ± 30	78 ± 29	26 ± 4	2.57 ± 1.20
Bipolar affectives	15	101 ± 16[2,3,4]	94 ± 29	23 ± 3[4]	4.11 ± 1.30[2,3,4]
Schizophrenic patients	18	124 ± 26	91 ± 30	28 ± 5[5]	2.77 ± 0.99
Control subjects	22	125 ± 16	90 ± 16	26 ± 4	2.90 ± 0.54

All results are expressed as means ± 1 SD. *APP+* acute polymorphic psychosis with psychosensory symptoms; *APP−* acute polymorphic psychosis without psychosensory symptoms.

[1]Reproduced from Fekkes et al. (1994) with permission; [2]$p < 0.05$ vs. control subjects; [3]$p < 0.05$ vs. atypical psychosis; [4]$p < 0.05$ vs. schizophrenic patients; [5]$p < 0.05$ vs. APP− (one-way analysis of variance).

The statistical test used was an univariate analysis of variance and a Student-Newman-Keuls procedure for individual variables. The significance level was set at 0.05 (two-tailed).

who had *not* been treated with antipsychotic medication during the month before this episode, blood for amino acid analysis was drawn from fasting subjects between 8 and 9 a.m.

The plasma levels of serine in the APP+ patients were significantly lower than in healthy controls (Table 3). The plasma taurine concentration in these patients was slightly elevated and the plasma methionine level was somewhat lower, although not statistically significant. The plasma serine levels in the APP+ patients were also significantly lower than in APP− patients, in patients with atypical psychoses and in schizophrenic patients. However, no differences were found between APP+ patients and patients with bipolar disorder (Table 3).

Since the plasma concentrations of the above mentioned amino acids were all different in the APP+ patients, it was decided to introduce a biochemical marker which takes all three amino acids into account, in order to increase the sensitivity in discriminating these patients. We did this by constructing the so-

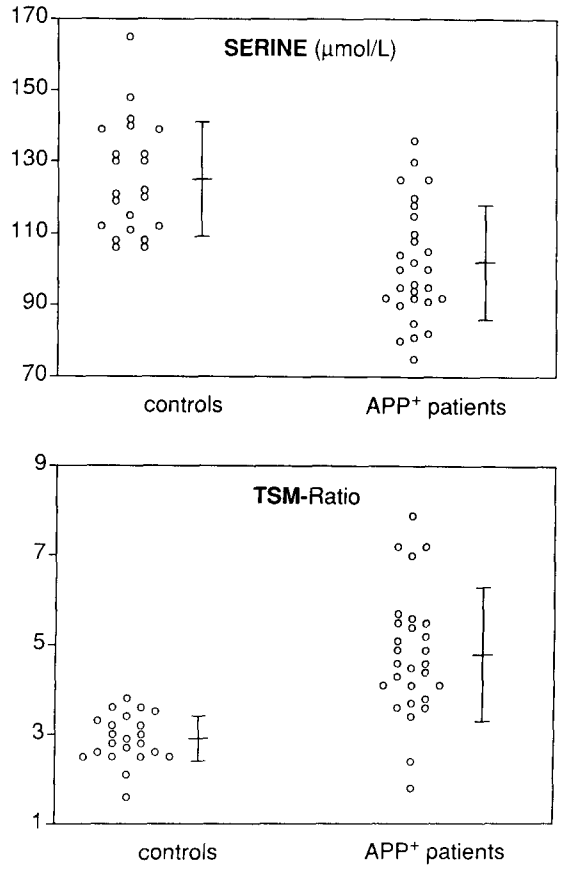

Fig. 2. Serine concentrations (in μmol/1) and TSM ratios in blood plasma of 28 APP+ patients and 22 healthy control subjects. *APP+* acute polymorphic psychosis with psychosensory symptoms. The error bars indicate the mean and SD. Blood was drawn before breakfast after an overnight fast. Reproduced from Fekkes et al. (1994) with permission

called TSM-ratio, which is defined as the ratio of 100 times the taurine concentration in plasma and the product of the plasma concentrations of serine and methionine. It was found that the TSM-ratio discriminated the APP+ patients with greater sensitivity (univariate analysis of variance: $F = 12.38$) than when using the plasma serine concentration alone ($F = 6.68$). However, the specificity was not better, because the TSM-ratio in the bipolar affective patients was only slightly lower (4.11 ± 1.30) than in the APP+ patients (4.80 ± 1.49).

The major finding of this study was that decreased plasma serine levels and increased TSM-ratio are state markers for the subgroup of episodic psychotic (APP+) patients (Fig. 2). An ungoing follow-up study not yet completed shows that these biological markers are also abnormal in APP+ patients during asymptomatic periods.

Therefore, the determination of serine and the TSM-ratio in the plasma of psychotic patients may be a useful diagnostic tool in patients with acute polymorphic psychoses.

Prevalence of APP+ in psychiatric in-patients

The prevalence of APP+ was investigated in 140 chronic psychiatric patients (64 women and 76 men). The medical records were studied retrospectively and the psychiatric syndrome was classified according to the Research Diagnostic Criteria (RDC; Spitzer et al., 1978) by two independent investigators (Rijn-van den Meijdenberg et al., 1994). After exclusion of the RDC-nonpsychotic categories, 102 patients whose descriptive and biochemical data of the RDC category are depicted in Table 4 were included. APP+ could be demonstrated in two patients, based on both clinical and biochemical criteria, i.e. lowered plasma serine concentration (cut-off limit: 82μmol/1) and increased TSM-ratio (cut-off limit: 2.72). In three patients APP+ was suspected to be present. Two of these patients met the biochemical criteria and when clinically re-evaluated, the characteristic symptoms of APP+ were

Table 4. Descriptive and biochemical data of RDC-psychotic-categories[1]

Diagnostic category	n	Sex male/female	Age	Serine (μmol/l)	TSM-ratio
Schizophrenia	50	29/21	46.5 ± 11.3	113 ± 28	2.15 ± 0.78
Schizoaffective disorder, manic type	7	3/4	50.9 ± 13.8	116 ± 26	2.40 ± 0.70
Schizoaffective disorder, depressed type	15	6/9	44.9 ± 10.2	119 ± 24	1.97 ± 0.60
Major depressive disorder	20	9/11	52.8 ± 10.1	107 ± 25	2.42 ± 0.83
Unspecified functional psychosis	10	4/6	45.3 ± 13.5	99 ± 21	2.56 ± 0.89
Healthy controls	17	7/10	34.6 ± 6.4	126 ± 22	1.72 ± 0.64

[1] Reproduced from Rijn-van den Meijdenberg et al. (1994) with permission.
All results are expressed as means ± 1 SD.

present, but less pronounced. In one patient, the characteristic clinical symptomatology of APP+ and an increased TSM-ratio were present, but the serine concentration was within normal range. Interestingly, four of these patients were classified in either the category "schizoaffective disorder, manic type" or "unspecified functional psychosis", two categories which overlap symptomatologically. In only one patient, suffering from a labile personality disorder, positive biochemical markers were found, whereas no symptoms of APP+ could be demonstrated. However, challenge tests have not been performed yet, but this retrospective investigation shows that in a psychiatric inpatient population APP+ patients can be clinically recognized.

The prevalence of APP+ in the 140 patients included in this retrospective study ranged between 1.4 and 3.6%.

Fibroblast experiments

Data obtained from plasma studies suggest an enzyme abnormality related to the metabolism of serine (Bruinvels et al., 1984). Among other things, an impaired conversion of glycine into serine was found. However, enzyme studies using fibroblasts obtained from APP+ patients did not reveal any enzymatic malfunctioning (Fekkes and Bruinvels, 1986). As these enzyme studies were performed with fibroblasts obtained from APP+ patients, the enzyme activities per se were measured. Thus, it is conceivable that in these patients some factor is present which is responsible for the disturbed metabolism of serine. Therefore, it was decided to subculture fibroblasts in a medium supplemented with patients' serum or normal human serum. When fibroblasts were subcultured in the presence of serum obtained from APP+ patients, the concentrations of both serine and methionine in harvested cells were lower than concentrations after culturing these cells with serum from normal controls. On the other hand, in the presence of patients' serum the concentration of taurine in the fibroblasts was increased (Fekkes et al., 1991). From these data it was concluded that there was some factor in the serum of APP+ patients that may be held responsible for the altered amino acid metabolism. The fact that the concentrations of serine and methionine were lower in the medium and in the fibroblasts in the presence of patients' serum, suggests that the serum factor may alter the metabolism of these amino acids and not their transport into the cell.

These findings suggest that the activities of serine hydroxymethyltransferase (SHMT) and cystathionine β-synthase, both serine metabolizing enzymes, are increased by the supposed serum factor. Measurement of these enzymes in the fibroblasts indeed showed that both enzymes had higher activities after subculturing with patients' serum (Table 5). Thus, the activation of the enzymes may occur due to a factor in the serum of the APP+ patients. The serum factor appears to be different from the cofactor pyridoxal 5'-phosphate, because addition of this compound increased the enzyme activities to the same extent, irrespective of the serum present during subculturing of the fibroblasts (Table 5).

Table 5. Serine hydroxymethyltransferase (SHMT) and cystathionine β-synthase activities in fibroblasts after subculturing in the presence of 10% normal or 10% APP+ serum[1]

Serum in medium	Cofactor during incubation	SHMT	Cystathionine β-synthase
10% APP+ serum	yes	5.96 ± 0.48 (6)[2]	0.577 ± 0.039 (6)[3]
10% normal serum	yes	4.80 ± 0.39 (6)	0.377 ± 0.015 (8)
10% APP+ serum	no	3.89 ± 0.11 (6)[4]	0.413 ± 0.054 (6)[5]
10% normal serum	no	3.22 ± 0.15 (6)	0.291 ± 0.031 (8)

[1] Reproduced from Fekkes et al. (1991) with permission.
Means ± SEM are expressed in nmol/min/mg protein with the number of sera tested in parentheses. Each serum was added to fibroblasts from a normal individual and from a patient, and the measured enzyme activities were averaged. The cofactor used for both enzymatic reactions was 1 mM pyridoxal 5′-phosphate.
Statistical significance of difference from 10% normal serum: [2]$p = 0.047$; [3]$p = 0.001$; [4]$p = 0.003$; [5]$p = 0.030$ (One-tailed Student's t-test).

Activation of cystathionine β-synthase results in higher formation of taurine and lower production rates of methionine, because its precursor, homocysteine, will now be used for the increased synthesis of taurine. Another consequence of this activation may be an accumulation of 5-methyl- and 5,10-methylene tetrahydrofolic acid (Fig. 1), due to a decreased availability of homocysteine. The activation of SHMT will also contribute to higher levels of 5,10-methylene tetrahydrofolic acid. Dissociation of this compound into tetrahydrofolic acid and formaldehyde may then be facilitated, which will eventually result in the formation of β-carbolines and isoquinolines, some of which are psychotogenic substances (Bruinvels et al., 1980; Pepplinkhuizen et al., 1980).

Conclusions

(1) Careful psychiatric diagnosing may reveal specific psychotic disorders characterized by an episodic nature, intense emotional states and in general a kaleidoscopic polymorphic clinical picture, classified as acute polymorphic psychosis (APP) according to ICD-10.

(2) Many patients with this diagnosis also suffer from psychosensory phenomena (APP+) and most of these patients exhibit a low plasma serine concentration and a high TSM-ratio, indicating a disturbed serine metabolism. These biochemical markers may be a useful diagnostic tool in discriminating APP+.

(3) In remitted APP+ patients oral challenge with serine induced characteristic dysperceptions and psychedelic symptoms.

(4) The prevalence of APP+ in psychiatric in-patients ranged between 1.4 and 3.6%.

(5) Measurement of the serine metabolizing enzymes serine hydroxymethyltransferase and cystathionine β-synthase in fibroblasts obtained from

APP+ patients did not reveal any abnormality. However, when fibroblasts were subcultured in the presence of serum obtained from APP+ patients, these enzymes showed an increased activity.

(6) So far, no other studies have been published on the occurrence of amino acid abnormalities in transient acute polymorphic psychosis.

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