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A Biochemical Basis for Psychotic Symptoms in Patients with Brain Dysfunction

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Summary. Thirteen brain dysfunctional patients with psychosis were compared to 11 brain dysfunctional patients without psychosis by EEG, CT scan and neuropsychological test abnormalities, and abnormalities in serine metabolism. None of the tests of conventional measures of brain pathology and pathophysiology significantly differentiated between the psychotic and nonpsychotic patients; only the last measure which has previously been shown to be a biochemical vulnerability factor for psychosis, was significantly different in the two groups. This study suggests that the brain pathology and pathophysiology per se are not significant factors that make such patients psychotic, but these patients are vulnerable to psychosis because of a biochemical abnormality.

Key words: OBS – Psychosis – Serine metabolism

Introduction

The incidence of psychotic symptoms (delusions, believed hallucinations) in patients with various brain pathologies vary from 0.05% (in multiples sclerosis) to 33% (in Picks disease) (Davison and Bagley 1969). In the general population the lifetime prevalence of psychotic illnesses is 3–5% (Robins et al. 1984). Why certain patients with brain dysfunction become psychotic when others do not, is a question not as yet clearly answered. It is generally assumed that psychotic and schizophrenic-like symptoms are associated with pathology in specific sites in the brain such as temporal lobes, the medial brain stem structures and the frontal lobes (Davison and Bagley 1969). According to one report, patients who become psychotic after right hemisphere infarcts show no particular predilection for pathology in any particular site in the brain when compared to patients with right hemisphere infarcts who do not become psychotic (Levine and Grek 1984). In that study the factor that differentiated the psychotic from nonpsychotic brain infarcted patients was the presence of antecedent generalized brain atrophy as evidenced by enlarged ventricles and widened sulci (Levine and Grek 1984). However, another study of patients with right hemisphere infarcts and psychosis has not uncovered such premorbid brain atrophy (Price and Mesulam 1985). Thus, neither the size, nor the location of pathology appear to be predominant factors in the etiology of psychosis. If neither the size nor the site of the brain pathology is an important antecedent to psychotic symptoms, it is reasonable to assume that in brain dysfunctional patients who become psychotic there is some other special factor which makes them vulnerable to psychosis.

In several studies (Waziri et al. 1983; Waziri et al. 1984; Wilcox et al. 1985; Waziri et al. 1985; Waziri and Mott 1986) on close to 300 psychiatric patients and normal controls we have found that psychotic patients regardless of diagnosis, have high plasma serine levels (PSL) and low serine hydroxymethyltransferase (SHMT) activity, as compared to nonpsychotic patients and normal controls. In these studies, age, sex, dietary habits and drug intake do not contribute to these findings. Because the PSL values are highly correlated to the activity of SHMT, the enzyme which catalyzes the major degradative pathway of serine metabolism, it is quite likely that the hyperserinemia in psychotics is largely secondary to the lowered SHMT activity in psychotic subjects. Also, we have evidence to suggest that the abnormal serine metabolism is a vulnerability factor and a trait marker for psychosis (Waziri et al. 1984). We have tested this hypothesis in a group of depressives with psychotic features and a group of depressives without psychotic features. The psychotic depressives have significantly higher PSL and lower SHMT activity than the nonpsychotic depressives (Waziri et al. 1985). In this study we have tested this hypothesis in brain dysfunctional (organic brain syndrome) patients with and without psychosis, to see whether abnormal serine metabolism can significantly differentiate the psychotics from the non-psychotics and whether other organic factors can be considered etiologically important in this differentiations.

Subjects and Methods

All the subjects were inpatients admitted to the University of Iowa Psychiatric Hospital. They carried the DSM-III (Diagnostic Statistical Manual, Third Revision, American Psychiatric Association, 1980) diagnoses of organic brain syndrome, with pathology and pathophysiology primarily in the brain. The history of brain pathology and pathophysiology in these subjects were established to be antecedent to, or coeval with, the psychiatric symptoms. Patients who had psychiatric illnesses before the development of brain dysfunction were not included. Most of the data on the presence or absence of psychosis and other psychiatric problems were obtained by clinical interview and application of the Brief Psychiatric Rating Scale, utilizing the items relevant to psychosis (Waziri et al. 1984). Two severely demented and aphasic patients (No. 8, Table 1a and No. 7, Table 1b) could not provide direct information. Such information was obtained from the records of

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Table 1a. Brain dysfunctional psychotics

No.	Sex	Age	Cause of brain dysfunction	MMSE Score	EEG Abnormality		CT Scan Abnormality		Neuro-psych. abnor-mality	Reason for admission
					De-gree	Site	De-gree	Site		
1	F	68	Unknown etiology	26	3	Diffuse	3	Diffuse	2	Delusional talk & behavior
2	F	73	Alzheimer's	21	3	Diffuse	3	Diffuse	4	Delusional behaviour
3	F	46	Epilepsy	28	3	L > R	1	Diffuse	ND	Depression & delusions
4	F	40	Head injury	29	3	L > R	1	L = R	2	Delusions, hallucinations & violent behavior
5	M	21	Brain atrophy of unknown etiology	27	ND	–	2	Diffuse	2	Hallucinations & depression
6	F	55	Multi-infarcts	27	1	R > L	3	R > L	3	Delusions & hallucinations
7	F	19	Epilepsy	29	3	Diffuse	ND	–	2	Violent behavior & paranoid thoughts
8	F	68	Degenerative dementia	9	2	Diffuse	4	Diffuse	5	Aggression & delusions
9	M	47	Epilepsy	17	3	Diffuse	2	L > R	4	Hallucinations & delusions
10	M	54	Alzheimer's	27	2	Diffuse	0	–	1	Confusion & delusions
11	M	37	Epilepsy	30	3	L > R	0	–	2	Delusional behavior
12	M	23	Epilepsy	30	3	L > R	2	Diffuse	1	Depression & delusions
13	F	68	Alzheimer's	7	2	Diffuse	1	Diffuse	5	Confusion, delusions & hallusinations

ND = Not Done

Table 1b. Brain dysfunctional nonpsychotics

No.	Sex	Age	Cause of brain dysfunction	MMSE Score	EEG Abnormality		CT Scan Abnormality		Neuro-psych. abnor-mality	Reason for admission
					De-gree	Site	De-gree	Site		
1	M	29	Epilepsy	30	3	R > L	3	R > L	ND	Depression
2	M	21	Epilepsy	26	3	Diffuse	3	R > L	1	Obsessions & stereotypy
3	F	69	Mult-infarct	25	3	Diffuse	1	R = L	ND	Depression & agitation
4	F	32	Post-traumatic hydrocephalus	24	0	–	1	L = R	3	Violent behavior
5	M	62	Alzheimer's	28	2	Diffuse	2	L > R	ND	Irritability, tantrums & confusion
6	F	68	Brain infarct	26	2	L = R	2	L = R	ND	Delirium & agitations
7	F	73	Multi-infarct dementia	10	3	Diffuse	4	Diffuse	5	Depression & agitation
8	M	18	Hydrocephalus	27	2	R > L	3	L = R	2	Depression & conduct disorder
9	M	81	Alzheimer's	20	3	Diffuse	3	Diffuse	ND	Memory loss & agitation
10	M	66	Brain trauma	27	3	L = R	3	L = R	ND	Confabulation
11	M	26	Epilepsy	26	3	L > R	ND	–	ND	Violent outbursts

ND = Not Done

their previous clinical contacts either in our facility or other hospitals. In order to be included in the study, patients had to have been tested and found to have deficits or abnormalities, by at least two of the following measures. 1) Minimental Status Examination (MMSE) (Folstein et al. 1975) scores of 27 or less; 2) EEG abnormalities; 3) CT scan abnormalities and 4) Neurophsychological test deficits. Except for the MMSE scores which were recorded as such, other abnormalities were scored as follows: 0 – no abnormality; 1 – borderline; 2 – mild; 3 – moderate; 4 – sever; and 5 – marked. In the case of EEG's, the specialists from Neurology has scored these abnormalities blindly. Borderline to marked CT scan and neuropsychological abnormalities were scored by the first author on the basis of statements included in the reports by the radiologist and psychologist. There were a total of 24 patients, 13 were classified as psychotic and 11 as nonpsychotic. Only 2 of the 13 psychotics had a family history of a psychotic illness and only 1 of the 11 nonpsychotics had a fam-

ily history of a psychotic illness. There were no differences between the psychotic and nonpsychotics in the duration of the brain disease prior to the development of psychosis. The demographic and clinical characteristics of the psychotic and nonpsychotic patients are presented in Tables 1a and 1b, respectively. All statistical significances were arrived at by *t*-test.

Laboratory procedures. Fasting venous blood was obtained in EDTA containing tubes between 7:30 a.m. and 8:00 a.m. The blood was stored at 4°C for no more than 3 h. The blood was then centrifuged at 760 × g for 15 min to separate the platelet rich plasma from the blood cells. The platelet rich plasma was then centrifuged at 16,000 × g for 3 min and the platelet-free plasma was either immediately assayed for amino acids and SHMT activity or stored at −70°C for future use.

Plasma amino acids were assayed by gas chromatography with techniques described earlier (Zumwalt et al. 1971). In this technique we added 125 nmoles of 2-aminobutyric acid as internal standard to 0.5 ml of plasma which was then acidified by 1 ml of 5% trichloroacetic (TCA) to precipitate the proteins. The mixture was vortexed and kept on ice for 10 min. It was then centrifuged at 16,000 × g for 3 min, and the supernatant passed through a column (0.6 × 5 cm) of acidified and washed Amberlite CG-120. Unretained materials were removed by washing the column with 5 bed volumes of water. The amino acids were then collected by eluting with 2 bed volumes of 2N ammonium hydroxide. The amino acids in the evaluate were derivatized, by drying an aliquot of the eluate, esterifying with 3N HCl in n-butanol, and acylating with trifluoroacetic anhydride in methylene chloride. The residue was dissolved in dry ethyl acetate and injected into the GC column (1.6–1.8 meters long, 2.6 mm i.d.) packed with Tabsorb (Regis Chemical Co., Morton Grove, IL USA). The temperature program in the GC (Shimadzu, Model CG-8) started at 110°C and increased at 6°C/min to a temperature of 210°C and held for 8 min. Peak measurements and concentration determinations were done by a Shimadzu C-R1A integrator in the internal standard mode.

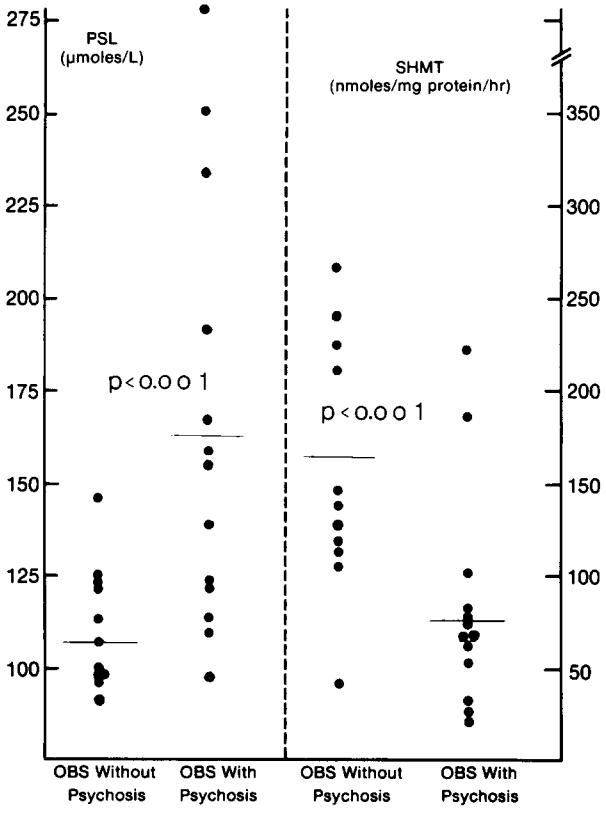

Fig. 1. Scattergram of plasma serine levels (PSL) and serine hydroxymethyltransferase (SHMT) activity in organic brain syndrome (OBS) patients with and without psychosis. Significance by *t*-test

Plasma SHMT activity was assayed by adding half a milliliter of plasma to a slurry of 30% CM Sephadex gel in 20 m*M* phosphate buffer at pH 7.4. This mixture stood with occasional gentle mixing at room temperature for 10 min. The mixture was then centrifuged, the supernatant discarded, and the gel washed and centrifuged three times with 0.5 ml of 20 m*M* phosphate buffer (pH 7.4). After the last centrifugation and decanting of the supernatant, 0.6 ml of 200 m*M* phosphate buffer (pH 7.7) was added to the gel, which was then mixed by inversion at room temperature for 5 min. Following centrifugation at 16,000 × g for 2 min, the supernatant was retained as the enzyme solution. The protein content was determined by the method of Bradford (Bradford 1976). This partial purification of the enzyme increased its activity by 30 times relative to the enzyme in the plasma. The substrate/cofactor mixture for the assay was prepared by mixing 0.2 ml of water, 0.1 ml of 40 m*M* serine and 0.1 ml of an aquaeous solution containing 4 m*M* tetrahydrofolate, 2.5 m*M* pyridoxalphosphate and 57 m*M* 2 mercapoethanol. This solution was kept warm at 37°C. Then 0.4 ml of the warm substrate/cofactor solution was added to 0.6 ml of the enzyme solution. A 0.4 ml aliquot was removed immediately and mixed with 1 ml of 5% TCA containing 20 nmoles of 2-aminobutyric acid (as internal standard). This procedure stopped the enzyme activity. The remainder was incubated at 37°C for 15 min. Another 0.4 ml aliquot was removed and the reaction stopped as above. Both aliquots were then processed for amino acid analysis by GC as described previously. The glycine present in the first aliquot was subtracted from the second and enzyme activity expressed as nmoles (glycine)/mg protein/h. All laboratory assays were done blind to the clinical characteristics of patients.

Results

The diagnostic and clinical characteristics of the psychotic and nonpsychotic patients are presented in Tables 1a and 1b, respectively. Neither of the two most frequently observed diagnostic categories, dementia and epilepsy, tended to be signifi-

Table 2. A comparison of psychotics and nonpsychotics in terms of various clinical factors

	Age	Sex (M/F)	MMSE	EEG Abnorm.	CT Abnorm.	Neurob. Abnorm.	PSL	SHMT
Psychotics	47.6 (18.9)	5/8	23.6 (7.8)[a]	2.7 (0.7)	2.6 (2.7)	2.8 (1.4)	164.9* (55.7)	76.8* (43.7)
Nonpsychotics	47.7 (26.4)	7/4	24.4 (5.4)	2.4 (0.9)	2.5 (0.9)	2.7 (1.7)	108.5 (33.7)	160.3 (67.9)

[a] Mean (S.D.)
* $P < 0.001$ (Difference between psychotic and nonpsychotic patients.), by *t*-test

cantly associated with either psychotic or nonpsychotic groups. Also, the site of the abnormality, in terms of right or left hemispheric location, was not significantly related to the presence or absence of psychosis. Of the four measures of brain dysfunction, MMSE, EEG, CT scan and neuropsychologicals, none significantly differentiated between psychotics and nonpsychotics (Table 2). Figure 1 is a scattergram of the values for PSL and SHMT in the psychotic and nonpsychotic patients. There were no significant age or sex differences between the two groups. In the psychotics, PSL was 164.9 (55.7) [mean (s.d.)] μ*M*/ml, while in the nonpsychotics PSL was 108.5 (17.9) μ*M*/ml. This difference was highly significant ($P < 0.001$). Plasma SHMT activity in psychotics was 76.8 (43.7) nmoles/mg protein/h. In nonpsychotics SHMT activity was 160.3 (67.9). This difference was also highly significant at $P < 0.001$ (Table 2).

Discussion

In this study as in our previous studies we found that PSL and SHMT activity were able to differentiate between psychotic and nonpsychotic subjects. In a recent report Perry and Hanson (1985) did not find that PSL in schizophrenics was different from a group of normal controls. We initiated studies to find the reason for this discrepancy. Perry and Hansen had used the classical amino acid analysis (AAA) of cation exchange chromatography, whereas we had used the GC for our serine assays. Perry and Hansen had suggested that the plasma of psychotics may have a substance that co-elutes with serine when assayed by GC. Consequently we have looked at the plasma of 15 psychotics and nonpsychotics both by GC and HPLC. The point by point correlation between PSL derived by GC and HPLC was 0.838 ($P < 0.0001$). HPLC analysis of PSL from 9 psychotic patients and 10 normal controls gave PSL values of 120 (10.4) nmoles/ml and 86.2 (11.5) nmoles/ml respectively. These values were significantly different ($P < 0.0005$). There is no evidence in the literature that two substances would co-elute simultaneously when assayed by two completely different chromatographic techniques. Another possibility, that the protein precipitation by trichloroacetic acid (TCA) used in preparation of plasma amino acids for GC and HPLC analysis, would release serine loosely bound from some proteins in the plasma of psychotics had not been ruled out. We therefore looked at the plasma of 8 psychotic subjects and 10 nonpsychotic subjects (stored for more than 6 months), where proteins were removed by addition of TCA or by ultrafiltration. The resultant amino acids from both techniques were assayed by HPLC. The linear regression analysis of serine values from all 18 subjects had a slope of 1.2416, an intercept of −0.3486 and correlation coefficient of 0.9841. This correlation was significant at $P < 0.0001$. The PSL of 8 psychotics determined by the TCA and ultrafiltrate techniques were 142.3 (50.3) and 118.9 (39.8) n*M*/ml respectively; while the PSL of 10 nonpsychotics by TCA and ultrafiltrate was 96.8 (12.7) and 80.4 (11.7) n*M*/ml respectively. By both techniques the differences between psychotic and non-psychotics was significant at $P < 0.025$. At this time we have no explanation for the discrepant findings of Perry and Hansen (1985) who used the ion exchange chromatography technique for assay of PSL. The use of these different techniques giving similar results in out laboratory make it unlikely that the PSL as measured by GC give artefactually higher PSL's in psychotics. Our finding of decreased activity in the SHMT of psychotics further strengthens the validity of our finding.

In this study as we had expected, high PSL and low SHMT activity significantly differentiated between the psychotic and nonpsychotic brain dysfunctional patients. On the basis of a previous report (Levine and Grek 1984) which had shown premorbid generalized brain atrophy in patients who became psychotic after right hemisphere infarcts, we had expected greater CT scan abnormalities in the group of our patients who were psychotic. This expectation was not fulfilled in this study. Neither was there a significant difference between EEG abnormalities and intellectual function tests of the psychotics and nonpsychotics. As in our previous studies, age and sex were not important variables, although there were more females in the psychotic and more males in the nonpsychotic groups. Had we limited ourselves to conventional tests of brain dysfunctions and not done PSL and SHMT assays, this study would we been inconclusive in regard to the etiology of psychosis in brain dysfunctional patients.

The exact role of abnormal serine metabolism in the pathogenesis of psychosis is unknown. Some of the putative metabolic points at which abnormal serine metabolism may exert a role in the emergence of psychotic symptoms, could be understood putatively in the context of the hyperdopaminergic hypothesis of psychosis (Carlsson 1978; Haracz 1982). Serine is a nonessential amino acid, present ubiquitously in many body tissues as well as in plasma. The metabolism of serine via SHMT provides glycine and 1-carbon units which are widely utilized in the body (Mudd and Poole 1975). These one carbon units are involved in the synthesis of thymidylate, adenosine and the methyl groups for S-adenosylmethionine. Its importance in the central nervous system is attributable to its being the sole precursor of the inhibitory neurotransmitter glycine (Daly and Aprison 1974) which also modulates the release of dopamine (Leviel et al. 1979). Glycine and the 1-carbon units are main component sources for the synthesis of adenosine (Henderson 1972) which modulates the release of dopamine as well as other neurotransmitters (Snyder 1985). The 1-carbon units are used in several metabolic processes, important amongst these being the methylation of catecholamines, indoleamines and phospholipids in the brain. In the context of the dopamine hypothesis, diminished glycine and 1-carbon production could play a role in the etiology of psychosis since both glycine and adenosine are potent presynaptic inhibitors of dopamine release. Also, the methyl groups derived from serine metabolism are utilized by catechol-0-methyltransferase, which inactivates intrasynaptic dopamine. The methylation of phospholipids may affect the sensitivity of membrane dopaminergic receptors (Axelrod 1982). At this time there is to direct evidence that any one or a combination of these metabolic loci in the brain are involved in the pathogenesis of psychosis.

Since the beginning of this century psychiatrists have classified psychotic illness as either "organic" or "functional". Organic psychoses have been so designated because patients, in addition to manifesting psychotic symptoms, also show some evidence of brain dysfunction such as disorientation and memory problems. This dichotomy has served a heuristic and probably a practical purpose, such that the organic psychoses when encountered have been further investigated for the cause of their psychoses by investigating the metabolic, toxic, chemical, anatomic or electrophysiologic abnormalities which affect the brain in these conditions. The removal and/or

amelioration of these abnormalities has frequently resulted in the removal or amelioration of psychotic symptoms, strengthening the concept of a causal relationship. However, on a conceptual level it is hard to justify a dichotomization between "organic" and "functional" psychoses. At one level when we refer to a psychosis as organic, we assume that we know the etiology of the psychosis while when we refer to a psychosis as functional, we submit that we do not know the etiology. Nevertheless, in both types of psychoses the specific treatment for the psychotic symptoms is most often the same, viz. neuroleptics. A problem which was alluded to in the beginning of this article, relates to our lack of knowledge in respect to the reasons as to why some individuals with certain brain pathophysiology or pathology develop psychosis, which we refer to as organic in origin, while other subjects, ostensibly with the same brain pathophysiology and pathology, do not become psychotic. In such a situation obviously then we have to consider the presence of some other factors which are necessary but insufficient for the production of psychosis. It is possible that the necessary factor(s) predisposing to psychotic symptoms would remain dormant and unknown until the organic factors (cerebral pathology) become extant, resulting in the manifestations of psychosis, and appearing as if the psychosis was caused by these organic factors.

It is known that certain types of brain diseases such as temporal lob epilepsy (Gibbs 1951; McKenna et al. 1985) or Alzheimer's dementia (Liston 1979), and brain pathology or pathophysiology lateralized to the dominant hemisphere (Sherwin et al. 1982) are much more associated with psychosis than other types of brain illnesses. There is a possibility that the pathology in these conditions is specifically affecting brain structures involved in the production of psychotic symptoms. It is also conceivable that the abnormal serine metabolism as a factor predisposing to psychosis may also be etiological in the development of pathology in brain areas previously found to be associated with psychosis. At present, there is not enough evidence to support either one of these postulates.

In this study, neither EEG nor the CT scan abnormalities lateralized significantly to the left hemisphere in psychotics. The small numbers and the diverse diagnostic categories may have not allowed for a relationship between psychosis and left sided abnormalities to emerge. These other relationships notwithstanding, our studies suggest that there is a unitary basis for vulnerability to psychotic symptoms in both the "functional" psychoses such as schizophrenia, mania, paranoia and the organic psychoses of various etiologies. Although it is quite possible that pathology in a specific brain site may produce psychosis, our studies suggest that by and large, when brain dysfunctional patients become psychotic, they do so not because of brain pathology at a specific site or of a particular severity, but because they have a lowered threshold or a higher vulnerability to psychosis due to a biochemical abnormality.

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