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PLATELET MAO ACTIVITY IN SUBGROUPS OF SCHIZOPHRENIA

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SUMMARY

Platelet MAO activity was estimated in 60 male drug free schizophrenics, 36 male drug free manics and 30 male normal healthy controls by Radio Isotopic Technique using ^{14}C Tryptamine Bisuccinate as substrate. There was no significant difference between the enzyme activity in the schizophrenic, manic and control groups. Platelet MAO activity in the disorganized catatonic and paranoid schizophrenics was significantly lower as compared to the enzyme activity in the manic and healthy control group. Platelet MAO activity appears to be related to subgroups of schizophrenia disorganized, catatonic and paranoid. Limitations and scope for future research have been outlined.

A consistent biological marker for schizophrenia would be welcome because it could serve as a validating criterion in sorting out the diagnostic puzzle surrounding this disease. Reduced platelet monoamine oxidase (MAO) activity has been felt to be a possible 'genetic' marker for schizophrenia because of the results of a study (Wyatt et al., 1973) on monozygotic twins discordant for schizophrenia. This study found that both the schizophrenic twin and his healthy co-twin had reduced platelet MAO activity indicating that the finding was not due to hospitalization, psychoactive drugs or other secondary effects of the illness. This study stimulated much subsequent work. Whilst many studies (Berger et al., 1978; Wyatt et al., 1978; Potkin et al., 1978; Sen Gupta et al., 1981) have replicated the above findings, some others (Brockington et al., 1976; Gupta et al., 1985) have not. Many potential sources of variability could have accounted for the discrepancy in the findings of previous authors. In view of the wide differences in the findings reported, attempts have been made to determine whether decreased platelet MAO activity is related to any subgroup of schizophrenia.

Acute schizophrenia as a group was not found to differ from control subjects (Friedman et al., 1974; Carpenter et al., 1975). Meltzer and Stahl (1974) observed decreased MAO activity in acute schizophrenics only when octapine and tryptamine were used as substrates, otherwise they had normal enzyme activity. Platelet MAO activity was lowered in schizophrenics which was more marked in chronic then in acute cases (Zeller & Davis, 1980). Paranoid schizophrenics have been reported in many studies, to have lowered platelet MAO activity (Potkin et al., 1978; Schildkraut et al., 1976; Van Valkenburg & Growe, 1978) however Berger et al., (1978), Gupta et al., (1985) could not confirm it. Auditory hallucinations have been observed to be associated with low platelet MAO activity in schizophrenic patients (Schildkraut et al., 1976). Although this could not be replicated subsequently (Gupta et al., 1985). A positive relationship with global prognostic score and platelet MAO activity has been reported (Gruen et al., 1982). Schizophrenics

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with positive symptoms (thought disorder, hallucination or delusion) did not differ from patients with negative symptoms (flattening of affect and mutism) (Brockington et al., 1976).

A neglected and poorly understood aspect of psychiatric correlates of psychiatric disorders is that not only low but also high platelet MAO activity appears to be related to psychopathology (Schalling et al., 1987). Another important observation has been that a small percentage of 'normal controls' have low MAO levels, well below the mean of the patient group (Buchsbaum et al., 1976). Furthermore, recent findings suggest that very low or very high platelet activity is associated with personality profiles linked with vulnerability to various psychiatric disorders. The intermediate group, on the other hand, is associated with higher scores on conformity scales and lower scores on anxiety and hostility scales and is presumably 'more normal' (Schalling et al., 1987). It is regretable that previous studies have not paid attention to this aspect while selecting controls.

It is apparent that more investigations are required in schizophrenics with better control of several variables, to identify the subgroup of schizophrenics with altered MAO activity and what, if any, physiological significance this might have. The present study was undertaken with the following aims:

1. To study and compare platelet MAO activity in schizophrenics with that in manics and control subjects.
2. To find out whether platelet MAO activity is related to any subgroup of schizophrenia.

Material & Methods

Sixty male schizophrenics diagnosed as per DSM-III (American Psychiatric Association, 1980) between 16-50 years of age were selected from the out patient psychiatric section of the University Hospital, B.H.U., Varanasi. These patients had not received any drugs in the past 2 weeks, no electroconvulsive therapy in the past 6 months, had no history of alcohol or drug abuse in the past 6 months, had no evidence of an organic mental disorder or a physical illness requiring medication or anaemia with Hb < 10 gm%, and did not have past or family history, in first degree relatives, of an affective or schizo affective illness.

Thirty six male manics (psychotic controls) diagnosed as per DSM-III, matched with the schizophrenic group with regard to age and haemoglobin, were selected from the out-patient psychiatric section of the University Hospital B.H.U. These patients had not received any medication (including neuroleptic and lithium) in the past 2 weeks, no electroconvulsive therapy in the past 6 months, had no history of alcohol or drug abuse in the past 6 months, had no evidence of an organic mental disorder or a physical illness requireing medication and did not have a past or family history in first degree relatives of a schizophrenic or a schizoaffective illness.

Thirty male normal healthy donors (normal controls), matched with the patient group with regard to age and haemoglobin were selected from the blood donors attending the Blood Bank of the University Hospital, B.H.U. These subjects did not have any evidence of a physical illness requiring medication, history of a neuropsychiatric illness (Migraine, Huntington's chorea, Schizophrenia, Affective Disorder, Schizo-affective disorders etc.) in the subject or his first degree relatives or a history of alcohol or drug abuse in the past 6 months.

Procedure:

The patients were hospitalized and kept drug free. They were evaluated on a structured proforma which included details of psychiatric history and mental status and physical examintion. 20 ml of fasting venous blood was collected between 9-11 A.M.

through vene puncture in heparanized polypropylene tubes, from each subject, and immediately placed in ice. Platelet rich plasma (PRP) was prepared within 3 hours by sequential centrifugation of the sample at 175,000 and 600g for 10 minutes each at 4^0C and supernatant PRP obtained, after each centrifugation was pooled. Subsequently, the PRP was centrifuged at 3000g for 5 minutes to obtain platelet pellets. Platelet pellets were stored at 80^0C till the time of assay, but never for more than one week. Platelet protein was estimated by Lowry's Method (Lowry et al., 1951). Finally, MAO activity was estimated by Radio Isotopic Technique, using ^{14}C Tryptamine Bisuccinate as the substrate,. All estimations were done in duplicate and the mean taken. Platelet MAO activity was expressed in micromoles of substrate per milligram of protein per hour. Estimators were blind to the identity of the samples. Method and sample variation (calculated as the difference between the paired samples divided by the mean) was ±5% for duplicate samples from the same blood specimen and ±16% when 2 blood samples were obtained from 15 healthy controls at an interval of one week. The coefficient of variation was 4% for duplicate samples from the same blood specimen and 9% for blood samples taken one week apart.

Platelet MAO activity in the healthy control group ranged from 9.5-0.5 n mol/mg protein/h. The subjects with platelet MAO in the upper and lower decile were excluded as recent work has suggested that it is the intermediate group which is presumably more normal (Schalling et al., 1987). Thus 26 healthy controls were available for final analysis. The data was analysed by Chi square test, analysis of variance, student 't' test and least significant difference (multiple 't' test).

Results

There was no significant difference between the schizophrenic, manic and healthy control groups with regard to age and haemoglobin (Table-I).

No significant difference was observed between the platelet MAO activity in the schizophrenic, manic and healthy control groups (Table-II)

Subcategorisation of schizophrenics was done according to DSM-III. Platelet MAO activity in the disorganised, catatonic and paranoid schizophrenics was significantly lower as compared to the enzyme activity in the manic and healthy control groups (Table-III).

TABLE-1 Sample Characteristics

Variables	Schizo. (N=60)	Manics (N=36)	Controls (N=26)
Age (in yrs.)			
16 – 25	29 (48.4)	17 (47.2)	13 (50.0)
26 – 35	8 (38.3)	13 (36.1)	10 (38.5)
36 – 50	8 (13.3)	6 (16.6)	3 (11.5)
	X^2=0.38, d.f.=4, N.S.		
Hb (in gm %)			
12 – 13	14 (23.3)	9 (25.0)	7 (26.9)
13 – 14	38 (63.3)	23 (63.9)	15 (57.7)
14 – 15	8 (13.3)	4 (11.1)	4 (15.4)
	X^2=0.13, d.f.=4, N.S.		

Figures in parenthesis indicate percentage

TABLE-2 Platelet MAO Activity (in n mol/mg protien/h) in various groups

	Mean	s.d.
Schizo.(n=60)	3.40	2.06
Manics (n=36)	3.77	2.68
Controls (n=26)	4.06	1.16

F=0.967, N.S.

TABLE-9 Platelet MAO Activity (in n mol/mg protein/h) in subtypes of schizophrenics, manics and controls

	Mean	s. d.
Schizophrenia		
Undiff. (n=36)	4.19	2.20
Paranoid (n=16)	2.37	1.02
Cata. (n=8)	2.29	0.96
Disorganised (n=6)	1.87	1.39
Manics (n=36)	3.77	2.68
Control (n=26)	4.06	1.16

F=3.09, $p < .05$, LSD=1.038

10 schizophrenics had received neuroleptic drugs for variable periods (3 months – 1½ years)., but were drug free at the time of inclusion in the study. No significant difference was found between the platelet MAO activity of treated and never treated schizophrenics and controls ($t=0.73$; d.f.=58; $p < 0.5$).

Discussion

The present study was conducted on 60 schizophrenics, 36 manics (psychotic controls) and 30 normal healthy controls in which platelet MAO activity was determined by Radio Isotopic Technique using ^{14}C Tryptamine Bisuccinate as the substrate. Special care was taken to control the variables that might be related to platelet MAO activity.

No significant difference in the platelet MAO activity was observed between the patient group (schizophrenics) and the two control groups (manics and healthy controls). These observations are in conformity with the earlier reports (Brockington et al., 1976; Gupta et al., 1985). Some studies (Brockington et al., 1976; Berger et al., 1978; Wyatt et al., 1978; Sen Gupta et al., 1981) however, have reported a significant reduction in platelet MAO activity in chronic schizophrenics. Many potential sources of variability could have accounted for the discrepancy in the findings of previous authors. An important source of variance lies in the distribution of subgroups of schizophrenics in different populations. An attempt was made to find out whether the decrease in MAO activity was related to any subgroup of schizophrenia. It was observed that the disorganized, catatonic and paranoid subgroups of schizophrenia had significantly lower platelet MAO activity as compared to undifferentiated schizophrenics, manics and healthy controls. Normal activity in the manic group suggest that the lowered enzyme activity observed is not a non-specific change, but rather specific for certain subcategories of schizophrenia. However, since the number of patients in these subgroups was small, the conclusions can be regarded as only tentative.

Platelet MAO activity was estimated in 16 paranoid and 19 chronic hebephrenic schizophrenics by Flurometric method using Kynuramine as substrate and was observed to be significantly reduced as compared to controls (Van Valkenburg and Crowe, 1978).

In several studies (Potkin et al., 1978; Schildkraut et al., 1976; Van Valkenburg and Corwe, 1978) an association between low platelet MAO activity and paranoid symptoms has also been reported. In a mixed group of schizophrenics, patients with persecutory and accusatory delusions and auditory hallucination had significantly lower platelet MAO activity than others who did not have these symptoms (Schildkraut et al., 1978). Retrospective and prospective studies conducted by Potkin and associates confirmed the association of low MAO, activity with the paranoid subgroup (Potkin et al., 1978).

In some studies, however, (Gupta et al., 1986) lowered platelet MAO activity in the paranoid subgroup could not be demonstrated. Why one paranoid group should differ from another is not immediately

apparent. The discrepant findings were possibly because of heterogenous diagnostic criteria and use of different substrate and techniques for MAO estimation. Studies which failed to demonstrate low platelet MAO activity may have included patients with relatively better prognosis, since platelet MAO activity in schizophrenics has been observed to correlate with global prognostic score (Gruen et al., 1982). Gupta and co-workers (1985) estimated platelet MAO activity by spectrophotometric method which was not sensitive enough to tap very low levels of MAO activity. They did not observe any enzyme activity in 4 patients (13%), 4 first degree relatives (13%) and one control (0.33%) and excluded these subjects from statistical analysis, which may have confounded the results. Besides, they did not collect fasting samples which is necessary since blood glucose levels have been found to correlate with platelet MAO activity (Demishch et al., 1979).

The present work suggests that some form of schizophrenia (disorganised, catatonic and paranoid schizophrenia) may be separate from other forms of schizophrenia and this difference may be related, at least in part, to biochemical characteristics.

Some of the limitations of the present investigation need to be mentioned. The study should be replicated in the different subgroups of schizophrenia with larger number of patients and controls. It would be necessary to undertake similar work on female subjects, taking measures to control for the phases of menstrual cycle because platelet MAO activity has been reported to be higher in females and to fluctuate during the pre and post ovulatory phase (Wyatt et al., 1979). Simultaneous processing of control and patient samples has been suggested since relatively minor changes in the procedure can markedly influence platelet yield and leucocyte contamination (White et al., 1976). This was not done in the present study because of practical difficulties.

The decrease in platelet MAO activity could be related to the cause of the illness or could simply be associated with the disorder. A causal relationship could be particularly exciting because many biogenic amine hypothesis of schizophrenia (the dopamine, transmethylation, phenylethylamine and norepinephine hypothesis) would be consistent with decrease in MAO activity (Wyatt et al., 1979). However, only an association has been established so far. Further research based on the 'Biochemical High Risk Paradigm' shall throw more light by transcending the dilemma of whether the biological abnormality observed is of etiological significance or the result of the disorder.

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