CENTRAL DOPAMINE AND SEROTONIN TURNOVER IN SCHIZOPHRENIA

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SUMMARY

Comparison of CSF HVA and 5-HIAA levels of 20 Schizophrenics and 9 non-schizophrenic controls revealed no statistically significant difference between HVA levels but the 5-HIAA levels were significantly less in Schizophrenics (p < 0.05) than in controls. The significance of these findings is discussed.

Dopamine hypothesis of schizophrenia, according to which schizophrenia occurs due to functional overactivity of dopamine first given by Carlsson and Lindquist (1963), is the most accepted hypothesis today (Matthysse and Sugarman 1978). In spite of so many indirect evidences in favour of this hypothesis (Yaryura-Tobias et al 1979, Matthysse and Lipinski 1975, Snyder et al 1970, Matthysse and Kety 1974, Siggins et al 1974, Bunney and Agahjanian 1975, Randrup and Munkvad 1974) there is no direct proof to support this hypothesis. Contrary to expectations, majority of the studies (Persson and Ross 1969, Bowers et al 1969, Rimon et al 1971, Post et al 1975) have shown no rise in C.S.F. HVA (which is the main metabolite of dopamine) and the same is true of studies employing probenecid technique (Bowers 1974 c, Post et al 1975, Subrahmanyan 1975). While these studies have failed to show any significant change in HVA, at least three studies (Ashcroft et al 1966, Bowers et al 1969, & Subrahmanyan 1975) have reported low base line 5-HIAA values in schizophrenic patients.

An evaluation of the existing studies (Ashcroft et al 1966, Persson and Ross 1969, Rimon et al 1971, Post et al 1975, Subrahmanyan 1975, Bowers 1973 and Bowers 1974 c) shows that the patient population in all the studies consisted of acute schizophrenics or chronic schizophrenics or acute and chronic schizophrenics. Whereas it is doubtful whether acute schizophrenia is actually related to schizophrenic syndrome or is closer to affective disorders (Winokur et al 1972, McCabe et al 1971), it is more or less proved that definite changes occur in pre- and post-synaptic dopamine receptors in chronic schizophrenics (Bloom 1975). Hence studies conducted on such a sample should be viewed with caution. Atleast in one study (Bowers et al 1969) even the diagnosis of patients is not clearly mentioned. Similarly two studies (Ashcroft et al. 1966 and Subrahmanyan 1975) have included even neurological patients among their control groups. In the study of Persson and Ross (1969) patients were not drug free at the time of investigation.

Furthermore, we could not come across
any study which controlled relevant variables like diet, drugs, motor activity, the spinal level of lumbar puncture and the amount of C.S.F. taken. We, therefore, decided to conduct a study in which all these variables are simultaneously controlled.

**Aim**

The present study has been part of another research project “A comprehensive Biopsychological Study of Functional Psychoses”. The present paper is concerned only with finding out the difference in the rate of central turnover of dopamine and serotonin in schizophrenic patients and controls.

**Material and Methods**

**A) Selection of the study population**

The population of the present study was drawn from the schizophrenic patients attending the Walk-in-Clinic, Department of Psychiatry, National Institute of Mental Health and Neuro Sciences, Bangalore. The initial diagnosis of Schizophrenia was made according to International Classification of Diseases – 9th version which is routinely used in our institute. However to avoid the diagnostic impression of ICD 9 each patient was reevaluated diagnostically on a structured proforma incorporating a set of four criteria. The first three criteria are meant to exclude the kinds of psychoses which according to Manfred Bleuler “are definitely not schizophrenic” (World Health Organization 1973). The fourth criterion was that recommended by Mark and Phillips (1973) for “rapid, easy and accurate diagnosis of Schizophrenia in a large group of suspected schizophrenic cases”. These four criteria were

1) Absence of significant precipitating factor at the onset of the illness.
2) Absence of any evidence of impairment in primary mental functions.
3) Absence of primary involvement of mood.
4) Presence of any two of the following
   a) Any of the Schneider’s first rank symptoms.
   b) Irrelevance or incoherence
   c) Incongruity of affect
   d) A continuous illness of more than one year duration with absent insight.

The fourth criteria also has the advantage of incorporating both acute as well as chronic patients in the study population because it provides a diagnostic weightage to the duration of schizophrenia (more than one year) and at the same time, allows one to diagnose schizophrenia even if the duration is less than one year.

Those patients who satisfied the above criteria were diagnosed as schizophrenia for purpose of the study. These schizophrenic patients were reevaluated against certain exclusion criteria, viz.,

1) Non-availability of explicitly written informed consent for participation in the study.
2) History of intake of any drug during the past one month because drugs like phenothiazines are known to affect the turnover of central neurotransmitters (Creese et al. 1978).
3) Uncooperative, excessively withdrawn, excited or suicidal patients.
4) Presence of physical illness as revealed by detailed history, physical examination and base line haematological (Haemoglobin %, total and differential leucocyte count and general blood picture) & urine (Albumin, sugar and microscopic) examinations. Wherever the presence of any physical illness was even remotely suspected, further investigations as deemed necessary (e.g., X-rays of various
part of body, electrocardiogram, electroencephalogram etc. were performed to rule out the possibility of an existing organic disorder.

5) Female patients (because of certain administrative problems, it was not possible to include female patients in the sample).

The schizophrenic patients who were included in the study (according to the aforesaid inclusion and exclusion criteria) were further sub-categorized into various subtypes of schizophrenia according to International Classification of Diseases - 9th version.

B) Selection of controls

Male patients diagnosed as cases of acute reaction to stress of neurotic intensity (diagnosed according to ICD-9 by a psychiatric consultant) were taken as controls for the study. These patients had not taken any drugs in the past one month and had no clinically discernable physical illness. They were treated with supportive psychotherapy and were included in the study when they had recovered completely.

C) Preparation of the patient population

All the subjects included (schizophrenic patients and controls) in the study:

a) were admitted in the inpatient section of the hospital.

b) were not given any drugs during the first seven days of hospitalisation.

c) Were provided with a long list of high monoamine containing dietary substances (e.g., banana, tea, cocoa, coffee, chocolate etc.) and were forbidden to take any of these food stuffs during the period of study because they are likely to increase the metabolites of the monoamines in the brain (Muscettola et al 1977).

d) were administered various psychological tests including Inpatient Multidimensional Psychiatric Scale (Lorr et al 1963) but the present paper is connected mainly with the biochemical parameters.

D) Collection of C.S.F.

1. All the patients were kept on bed rest for 18 hours prior to lumbar puncture because motor activity even four hours before lumbar puncture increases 5-HIAA & HVA levels (Post et al 1973 a) probably because of increased metabolism and increase intermingling of cisternal and subarachnoid C.S.F. (Post et al 1973 b) but if the patients are kept on bed rest for 18 hours before lumbar puncture, the prior activity does not affect the amine metabolite levels (Weiss et al 1974).

2. After 18 hours of rest, with aseptic precautions, lumbar puncture was done between L3 and L4 vertebrae and five ml. of C.S.F. was collected. The amount of C.S.F. collected was restricted to five ml only because withdrawal of larger amounts of C.S.F. may give falsely high values for H.V.A & 5 HIAA because of a high ventriculolumbar gradient for these metabolites. (Moir et al 1970). The level of lumbar puncture was kept constant in each case i.e., between L3 and L4 vertebrae so that the amine values in each case may be equally affected by the ventriculolumbar gradient for HVA and 5 HIAA.

Thereafter, the patients were given oral probenecid 100 mg/m² of body weight in 5 divided doses at two hourly intervals to block the transport of HVA and 5 HIAA from C.S.F. to blood. We gave such high doses of probenecid, because at lower doses of probenecid the 5 HIAA and HVA levels correlate with C.S.F. probenecid level (Korf and Van Praag 1971, Sjostrom 1972, Bowers 1974 d, Muizelaar and Oberink 1975) but at higher doses of oral probenecid e.g. 100 mg/kg of body weight,
such correlations do not exist (Perel et al. 1974). After the total dose of probenecid was administered, again a lumbar puncture was performed between L3 and L4 vertebrae and 5 cc of C.S.F. was taken.

The C.S.F. was collected into ascorbic acid vials which were immediately kept in deep freeze at -20°C.

C.S.F. 5-Hydroxyindoleacetic acid and homovanillic acid were determined by spectro-fluorometric methods using Amico-Bowman Spectrofluorometer.

**Results and Discussion**

**Study population**

Out of 146 schizophrenic patients only 20 patients satisfied all the criteria for inclusion in the study. While such a large number of rejections of patients shows the stringency of our criteria for selection of cases, it also reflects that the study population was highly selective and not representative of schizophrenic population attending the Walk-in Clinic. Because of this limitation, the results derived from the sample cannot be freely generalized on the schizophrenic population in general. The subcategories of schizophrenia (according to ICD-9) included in the study population were paranoid schizophrenia (n=10), catatonic schizophrenia (n=6) and hebephrenic schizophrenia (n=4). To highlight the homogeneity of the subtypes of schizophrenia, it may be mentioned that a DEC-10 system computer using the items of Inpatient Multidimensional Psychiatric Scale (Lorr et al. 1963) isolated the three diagnostic categories (Paranoid, catatonic and hebephrenic schizophrenia) with 100% concordance at a similar index of 0.89 from a broader psychiatric sample group of 30. The number of controls was 9. The individual values of C.S.F. H.V.A. and 5HIAA are given in Table 1.

**Analysis of C.S.F. 5 HIAA values**

As shown in Table 2, the baseline (pre-probenecid) 5 HIAA level was significantly higher in the controls than in the schizophrenic patients (p < 0.05). The post-probenecid 5 HIAA value also was significantly higher in the controls than in the schizophrenics (p < 0.05). However, there was no statistically significant difference between accumulation of 5 HIAA (difference between postprobenecid and baseline 5 HIAA value) in the two groups.

For the purpose of statistical analysis the schizophrenic population was divided into two groups paranoid schizophrenics and non-paranoid schizophrenics (catatonic schizophrenics and hebephrenic schizophrenics). As shown in Table 3 when the controls, paranoid and non-paranoid schizophrenics were compared, there was no statistically significant difference in baseline (preprobenecid) and probenecid induced 5 HIAA accumulation of the three groups.

As shown in Table 2 there was no statistically significant difference between the baseline, postprobenecid and probenecid induced accumulation of H.V.A. in the schizophrenics and the controls.

However, as shown in Table 3 when the controls, paranoid schizophrenics and non-paranoid schizophrenics were compared, the paranoid schizophrenics had significantly lower baseline HVA value than those of the nonparanoid schizophrenics and the controls (p < .01). There was no statistically significant difference between the preprobenecid HVA and probenecid-induced HVA accumulation among the three groups.

**Interpretation of Results**

Even though there are several reports against brain contribution of lumbar C.S.F. 5 HIAA (Bulat and Zivkovic 1971, Post...
| S.No. | Diagnosis                | 5 H.I.A.A. ng/ml | H.V.A. (ng/ml) |
|------|-------------------------|-----------------|----------------|
|      |                         | Base line       | Post probenecid | Base line       | Post probenecid |
| 1.   | Paranoid Schizophrenia  | 22.2            | 31.0           | 38.0            | 37.0            |
| 2.   | "                       | 14.0            | 28.0           | 35.0            | 28.4            |
| 3.   | "                       | 20.0            | 18.0           | 15.0            | 20.0            |
| 4.   | "                       | 24.0            | 34.0           | 22.0            | 38.0            |
| 5.   | "                       | 26.0            | 28.0           | 36.0            | 28.0            |
| 6.   | "                       | 18.0            | 45.5           | 38.0            | 48.0            |
| 7.   | "                       | 31.2            | 31.0           | 32.0            | 32.0            |
| 8.   | "                       | 24.0            | 38.0           | 17.0            | 16.0            |
| 9.   | "                       | 37.2            | 20.6           | 18.0            | 28.0            |
| 10.  | "                       | 20.6            | 32.0           | 28.0            | 30.0            |
| 11.  | Catatonic Schizophrenia | 34.4            | 10.0           | 42.4            | 45.0            |
| 12.  | "                       | 13.0            | 12.8           | 78.0            | 45.0            |
| 13.  | "                       | 35.0            | 20.0           | 48.0            | 45.0            |
| 14.  | "                       | 140.0           | 122.0          | 32.8            | 28.0            |
| 15.  | "                       | 92.0            | 108.4          | 38.0            | 32.0            |
| 16.  | "                       | 94.0            | 84.0           | 38.7            | 38.0            |
| 17.  | Hebephrenic Schizophrenia | 23.0           | 24.2           | 65.0            | 48.0            |
| 18.  | "                       | 13.0            | 14.0           | 65.0            | 50.0            |
| 19.  | "                       | 104.0           | 142.0          | 37.0            | 39.4            |
| 20.  | "                       | 83.2            | 120.4          | 34.1            | 35.4            |
| 21.  | Control                 | 38.0            | 60.0           | 44.0            | 43.0            |
| 22.  | Control                 | 65.0            | 20.4           | 40.6            | 48.0            |
| 23.  | Control                 | 29.0            | 62.0           | 74.0            | 79.0            |
| 24.  | Control                 | 60.0            | 65.5           | 50.0            | 95.0            |
| 25.  | Control                 | 22.0            | 101.0          | 42.0            | 38.0            |
| 26.  | Control                 | 172.0           | 172.0          | 36.6            | 32.2            |
| 27.  | Control                 | 200.0           | 171.0          | 32.2            | 28.0            |
| 28.  | Control                 | 118.0           | 178.0          | 35.0            | 35.0            |
| 29.  | Control                 | 78.6            | 188.4          | 45.0            | 35.0            |
Table 2
Comparison of CSF 5 HIAA and HVA in schizophrenics and controls

| Sl. No. | Biochemical parameter studied | Sl. No. | Biochemical parameter studied | Sl. No. | Biochemical parameter studied |
|---------|-------------------------------|---------|-------------------------------|---------|-------------------------------|
| 1.      | Baseline CSF 5 HIAA           | 2.      | Postprobenecid                | 3.      | Probenecid induced accumulation of 5 HIAA |
|         | M 86.9556 SD 63.4711          | M 113.1441 SD 64.3622 | M 47.1222 SD 44.3778 | M 44.3778 SD 12.3808 | M 48.1337 SD 23.1368 | M 3.7533 SD 12.3808 |
| 4.      | Baseline CSF HVA              | 5.      | Postprobenecid C.S.F. H.V.A.  | 6.      | Probenecid induced accumulation of H.V.A. |
|         | M 43.44 SD 37.1309            | M 48.195 SD 41.8482 | M 12.785 SD 4.3778 | M 37.9 SD 16.2158 | M 35.56 SD 9.5085 | M 2.34 SD 3.7533 |
|         | Controls > schizophrenics     | P < 0.05 | Controls > Schizophrenics    | No Significant difference p > 0.05 |

Statistical Significance (using students 't' test)

Table 3
Comparison of C.S.F. 5 HIAA and HVA in controls, paranoid schizophrenics and nonparanoid schizophrenics

| Sl. No. | Biochemical parameter studied | Mean (M) and standard Deviation |
|---------|-------------------------------|---------------------------------|
| 1.      | Baseline C.S.F. 5 HIAA         | Controls M 86.9556 SD 63.4711 |
| 2.      | Postprobenecid C.S.F. 5 HIAA   | M 113.1441 SD 64.3622 |
| 3.      | Probenecid induced accumulation of 5 HIAA | M 47.1222 SD 44.3778 |
| 4.      | Baseline C.S.F. HVA            | M 44.3778 SD 12.3808 |
| 5.      | Postprobenecid C.S.F. H.V.A.   | M 48.1337 SD 23.1368 |
| 6.      | Probenecid induced accumulation of H.V.A. | M 3.7533 SD 12.3808 |
|         | Statistical Significance       | Non paranoid schizophrenics M 63.16 SD 26.1885 |
|         |                                 | M 30.61 SD 54.2899 |
|         |                                 | M 6.89 SD 2.62 |
|         |                                 | M 27.9 SD 15.7797 |
|         |                                 | M 30.54 SD 15.7797 |
|         |                                 | M 2.64 SD 7.32 |
|         | (using F test)                  | Statistical significance       |
|         |                                 | No Significant difference p > 0.05 |
|         |                                 | No significant difference p > 0.05 |
|         |                                 | No significant difference p > 0.05 |
|         |                                 | No significant difference p > 0.05 |
|         |                                 | P < 0.01 paranoid < Non paranoid schizophrenics and controls |
|         |                                 | No significant difference p > 0.05 |
|         |                                 | No significant difference p > 0.05 |
|         |                                 | No significant difference p > 0.05 |

et al 1973, Garelis & Sourkes 1973, Young et al 1973), the bulk of evidence is in favour of a major brain contribution (Eccleston et al 1970, Tamarkin et al 1970, Curzon et al 1971, Sourkes 1973, Garelis and Sourkes 1973 and Aghajanian & Gallager 1975).

Likewise, some HVA release occurs from the cord also (Kessler et al 1976, and Bingham et al, 1975), but there is enough literature to suggest substantial brain contribution (Garelis & Sourkes 1973, Curzon et al 1971, Post et al 1973, Tamkarkin et al 1970).

From these evidences it can reasonably be inferred that lumbar C.S.F. 5 HIAA and HVA levels reflect cerebral serotonin and dopamine turnover respectively. Combining these facts, it can be inferred that:
1. The schizophrenics have lower central serotonin turnover than the controls ($P < 0.001$).

2. There is no statistically significant difference between the central serotonin turnover of the paranoid and non-paranoid schizophrenics.

3. There is no statistically significant difference between the central dopamine turnover of the control and the schizophrenic patients.

4. There is no statistically significant difference between the central dopamine turnover in controls, paranoid schizophrenics and non-paranoid schizophrenics.

5. Since probenecid induced HVA accumulation in paranoid schizophrenics is not significantly different from that of controls and non-paranoid schizophrenics but there is a statistically significant ($P < 0.01$) lower baseline HVA value in paranoid schizophrenics than in the controls or non-paranoid schizophrenics, it can be inferred that the active transport process responsible for extrusion of HVA from C.S.F. to blood is more active in paranoid schizophrenics than in controls or non-paranoid schizophrenics.

It is well known that certain hallucinogens like L.S.D. 25 have marked anti-serotonin action and this had at one time led to the hypothesis that schizophrenia occurs because of decreased cerebral serotonin activity (Woolley and Shaw 1954). The nature of hallucinations (auditory or visual) was however never mentioned. The hypothesis was later on rejected in favour of dopamine hypothesis of schizophrenia (Matthyssee and Sugarman 1978). In addition, the post mortem examination of schizophrenic brains did not show serotoninergic deficiency (Crow et al. 1979). However, from the results of International Pilot Study of Schizophrenia, it is well established that among all symptoms of schizophrenia, auditory hallucinations are the most valuable ones because they have high specificity (discriminatory power), high frequency (74%) and also a high reliability of 0.86 (Lehmann 1976). Taking into consideration the importance of auditory hallucinations in schizophrenia the fact that decreased serotonin activity can probably produce hallucinations and our observation that the brain serotonin turnover is significantly less in schizophrenics than in controls, we hypothesize that while decreased serotonin activity may not be of aetiological significance in schizophrenia than in controls, we hypothesize that while decreased brain serotonin activity may not be of aetiological significance in schizophrenia, it may possibly be a symptom formation factor in schizophrenia as far as hallucinations are concerned.

Eighteen of the twenty schizophrenic patients in our study had one or more types of auditory hallucinations (commenting voices, 3rd person auditory hallucinations or thought echo) and therefore, a statistical comparison of the C.S.F. 5 HIAA levels of patients with and without auditory hallucinations is not possible. A separate study which specifically compares the C.S.F. 5 HIAA levels in schizophrenic patients with or without hallucinations, may resolve the issue.

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