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Original Investigations

5-Hydroxyindoleacetic Acid (5HIAA) and Homovanillic Acid (HVA) Following Probenecid in Acute Psychotic Patients Treated with Phenothiazines

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Abstract. Lumbar CSF 5HIAA and HVA were measured following probenecid administration in acute psychotic patients before and during treatment with phenothiazines. Patients with more classical schizophrenic symptoms had higher values for 5HIAA/HVA than other psychotics, depressives, and inmate volunteers. Prior to treatment CSF 5HIAA, but not HVA, correlated significantly with several clinical items related to psychotic disorganization. Phenothiazine treatment produced significant increases in CSF HVA which could not be correlated with the dose of antipsychotic or antiparkinson drugs.

Key words: 5-Hydroxyindoleacetic Acid — Homovanillic Acid — CSF — Psychosis — Phenothiazines — Probenecid.

In recent years basic neuropsychopharmacologic research has emphasized the role of monoamine pathways in the central nervous system.One strategy designed to extend these observations to clinical populations has utilized the measurement of acid monoamine metabolites in cerebrospinal fluid (CSF). Some of the results and unsolved problems with this approach have been reviewed (Moir *et al.*, 1970; Bowers, 1972a). We report here a further application of these methods. Using lumbar CSF following probenecid administration, we have measured 5-hydroxyindoleacetic acid (5HIAA) and homovanillic acid (HVA), metabolites of 5-hydroxytryptamine (5HT) and dopamine (DA) respectively, before and during treatment of patients suffering from acute psychotic reactions who achieved satisfactory clinical remission following treatment with a single antipsychotic compound.

Methods

Twenty-five patients (ages 16—54, 16 females and 9 males) were admitted voluntarily to a clinical research unit for study and treatment of acute psychotic reactions. Nine patients, six females and three males, had been previously hospi-

talized for psychotic reactions, and the present admission was occasioned by a recurrence of psychotic symptoms. Sixteen patients had not been previously hospitalized. One patient had allegedly taken LSD one time eight months prior to becoming psychotic but apparently had functioned reasonably well in the interim. Two others had used marihuana occasionally although no present use seemed related to the onset of psychotic symptoms. Otherwise no history of drug use was obtained from this group of patients. Diagnostically these patients would be included in the "schizophrenic spectrum" with borderline or pseudoneurotic states excluded; however, we have intentionally defined the group by strict pharmacological criteria-remission of psychosis following administration of a single antipsychotic compound. No patient had received psychotropic drugs for at least two weeks before the first CSF sampling.

Two or three weeks after admission each patient was rated using the Brief Psychiatric Rating Scale (BPRS). Prior to discharge (2 to 6 months later) each patient was rated on the Stephens-Astrup prognosis scale (Stephens *et al.*, 1966) and was scored positive or negative according to the presence or absence of the first rank symptoms of Schneider (Mellor, 1970; Taylor, 1972). (We did not include the symptom category "delusional percept" since, in our experience, this symptom is present in nearly all psychotic syndromes.) The Stephens-Astrup items have been shown to have predictive value for outcome in follow-up studies with psychotic patients. A number of similar items are found in other valid clinical ratings of good and poor prognostic syndromes in psychosis (Robins and Guze, 1970). The Schneider first rank symptoms have been considered characteristic of "true" schizophrenia and correlate in the predicted direction with prognostic items in some studies.

Prior to the administration of a single anti-psychotic compound, probenecid (100 mg/kg) was administered orally in six divided doses over a 24 h period. This schedule is somewhat different from ones we have previously used and is more consistent with the recommendations of Tamarkin *et al.* (1970). Following the probenecid administration 5 ml lumbar CSF was obtained and frozen prior to the fluorimetric measurement of 5HIAA and HVA as previously outlined (Gerbode and Bowers, 1968; Bowers, 1972a). In most cases patients were then treated with chlorpromazine or trifluperazine in doses required to produce remission of psychotic symptoms. Benztropine was used as necessary to treat extrapyramidal side effects. When satisfactory clinical remission had been achieved at a stable drug dose so that psychosocial therapies could be usefully employed, the BPRS rating, probenecid administration, and CSF sampling procedures were repeated. The interval between the first and second CSF sampling was two to six months. Raters had no prior knowledge of the metabolite values. Patients suffering from unipolar depressive reactions and paid inmate volunteers provided control values for 5HIAA and HVA. The depressives were studied concurrently in the same research unit. The inmates were studied on a prison hospital ward. All patients and controls were placed on bed rest 24 h before the CSF sampling which was always performed between one and two p.m. No dietary precautions were taken since dietary fluctuations which occur in precursor amino acids (tryptophan and tyrosine) have not been shown to alter CSF 5HIAA and HVA in man. In nine psychotic patients we were able to obtain only one CSF sample.

Pretreatment values for 5HIAA, HVA, and 5HIAA/HVA in the total psychotic group and the two subgroups (Schneider positive and negative groups) were compared with similar values in the depressive and inmate groups (t test). All ratios were transformed to their square roots before the t test was applied. All t tests were two-tailed. Paired values were also compared in the total psychotic group and the two psychotic subgroups before and during treatment with antipsychotic drugs

(Wilcoxen matched pair signed ranks test). Metabolic values before and during treatment and changes in these values with treatment were correlated with drug dose in two separate groups, patients taking chlorpromazine (CPZ) and those taking trifluperazine (TPZ). The metabolite values before treatment were correlated with the comparable BPRS and Stephens-Astrup items (Pearsonian r). Mean total Stephens-Astrup scores were compared in the two Schneider groups (t test).

Results

Mean pre-treatment values for 5HIAA, HVA, and 5HIAA/HVA in the total psychotic patient group did not differ significantly from comparable values in the depressive or inmate group (Table 1). However, when the total psychotic group was divided (Schneider-positive and negative) some differences emerged. The 5HIAA/HVA ratio in the Schneider-positive group was significantly higher than that in each of the other three groups, although neither the 5HIAA nor the HVA values themselves were significantly different between the groups. [The higher HVA value in the Schneider-negative group was just short of significance compared to the Schneider-positive group ($p < 0.1$)]. The Schneider-negative group had a significantly higher mean HVA value and a significantly lower ratio than the inmate group. In the depressive group HVA was significantly higher compared to the inmates, a finding we have previously reported (Bowers, 1972b). The individual data for these groups are shown in Fig. 1.

Table 2 shows the individual metabolite values and the drug doses for the total psychotic group before and during treatment. The values

Table 1. Pretreatment values for 5HIAA, HVA, and 5HIAA/HVA following probenecid in the lumbar CSF of psychotics, unipolar depressives, and inmate controls

Patient group	5HIAA[a]	HVA[a]	5HIAA/HVA	P	
1. Psychotics (total)	67.4±32.7 (18)	107.7±49.8 (18)	0.66±0.34 (18)		
2. Psychotics (S-positive)	72.0±31.6 (11)	90.8±34.4 (11)	0.83±0.31 (11)	(5HIAA/HVA)	<0.005 vs 3 <0.02 vs 4 <0.05 vs 5
3. Psychotics (S-negative)	53.3±33.3 (7)	134.3±60.9 (7)	0.39±0.19 (7)	(HVA) (5HIAA/HVA)	<0.05 vs 5 <0.005 vs 5
4. Depressives	61.8±27.1 (19)	131.3±69.6 (19)	0.54±0.29 (19)	(HVA)	<0.05 vs 5
5. Inmates	57.1±15.3 (15)	92.9±27.3 (15)	0.64±0.15 (15)		

[a] Nanograms (free acid) ± standard deviation (number of subjects).

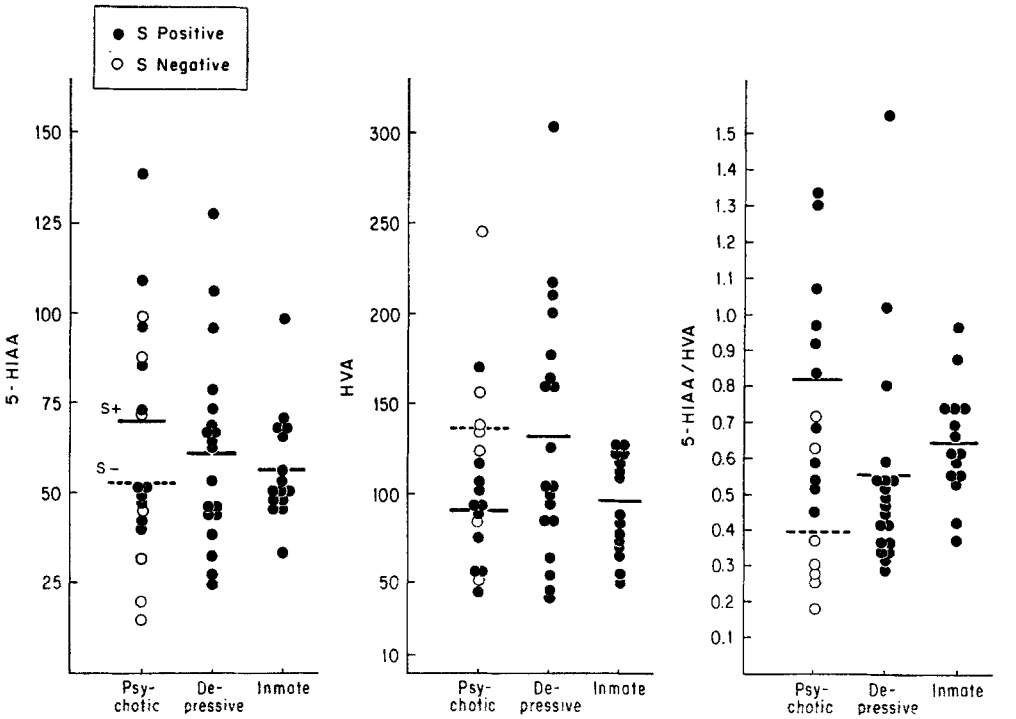

Fig. 1. Lumbar CSF 5HIAA, HVA, and 5HIAA/HVA following probenecid in acute psychotics (Schneider positive and negative), depressives, and imate controls

during treatment are significantly higher for HVA ($p < 0.005$) and lower for the ratio ($p < 0.02$). A significant increase in HVA during treatment with antipsychotic drugs occurred in both the Schneider positive ($p < 0.02$) and the Schneider-negative groups ($p = 0.05$). There were no significant correlations between drug dose and metabolite values (before treatment, during treatment, or change) for the groups treated with CPZ or TPZ. Nor were there significant correlations between these metabolite values and the doses of antiparkinsonian drug (benztropine) used to control side effects.

BPRS items related to psychosis which correlated significantly with metabolite values prior to treatment are shown in Table 3. 5HIAA appeared to correlate better than HVA with several items of the BPRS related to psychotic disorganization of mental content. Particularly noteworthy is the high correlation (0.78) between 5HIAA and "unusual thoughts" on the BPRS. A plot of these values is shown in Fig. 2. The

Table 2. 5HIAA, HVA, and 5HIAA/HVA following probenecid in psychotic patients before and during treatment with antipsychotic drugs

Patient	Schneider	Before treatment			Drug dose[a]	During treatment		
		5HIAA	HVA	5HIAA/HVA		5HIAA	HVA	5HIAA/HVA
1	Neg.	20	54	0.37	T-30, B-3	20	222	0.09
2	Pos.	97	117	0.83	C-600, B-1.5	60	154	0.39
3	Pos.	138	104	1.33	T-30, B-4	71	238	0.30
4	Pos.	74	57	1.30	C-600	35	30	1.17
5	Pos.	40	89	0.45	T-30, B-1.5	52	130	0.40
6	Pos.	53	77	0.69	T-10, B-2	41	41	1.0
7	Pos.	43	45	0.96	T-50, B-4	69	195	0.35
8	Pos.	53	90	0.59	—	—	—	—
9	Neg.	73	247	0.29	T-16, B-3	55	342	0.16
10	Neg.	47	157	0.30	—	—	—	—
11		—	—	—	H-6, B-4	43	300	0.14
12	Neg.	32	121	0.26	T-10, B-2	88	178	0.49
13	Neg.	99	139	0.71	C-300	35	96	0.36
14	Pos.	86	170	0.51	H-4, B-2	96	222	0.43
15	Pos.	48	91	0.52	T-40, B-4	81	128	0.63
16	Pos.	108	102	1.06	T-15, B-2	98	200	0.49
17	Neg.	87	137	0.63	T-30, B-3	98	181	0.54
18	Neg.	15	85	0.18	C-600, B-2	55	294	0.19
19	Pos.	52	57	0.91	T-15, B-1	79	214	0.37
$\bar{x}$		64.7	107.7	0.66		63.3	186.2*	0.44**
S.D.		32.7	49.8	0.34		24.2	85.3	0.28
S.E.		7.7	11.7	0.08		5.8	20.6	0.07
N.		18	18	18		17	17	17

[a] mg per 24 h; C is chlorpromazine; T is trifluorperazine; H is haloperidol; B is benztropine.

* $p < 0.005$. — ** $p < 0.02$.

mean BPRS scores before and during treatment were significantly different in the expected direction ($p < 0.001$). There were no significant correlations between pre-treatment metabolite values and the Stephens-Astrup scores. Because so few patients had relatively high Stephens-Astrup ratings, we could not compare metabolite values in good and poor

Table 3. Significant correlations between BPRS items, 5HIAA, and HVA before treatment

BPRS item	r (5HIAA)	r (HVA)
Unusual thoughts	0.78 ($p < 0.001$)	0.41 ($p > 0.05$)
Anxiety	0.58 ($p < 0.02$)	0.47 ($p < 0.05$)
Conceptual disorganization	0.46 ($p = 0.05$)	−0.02 (N.S.)
Suspiciousness	0.44 ($p = 0.05$)	−0.13 (N.S.)
Sum of items	0.46 ($p = 0.05$)	−0.13 (N.S.)

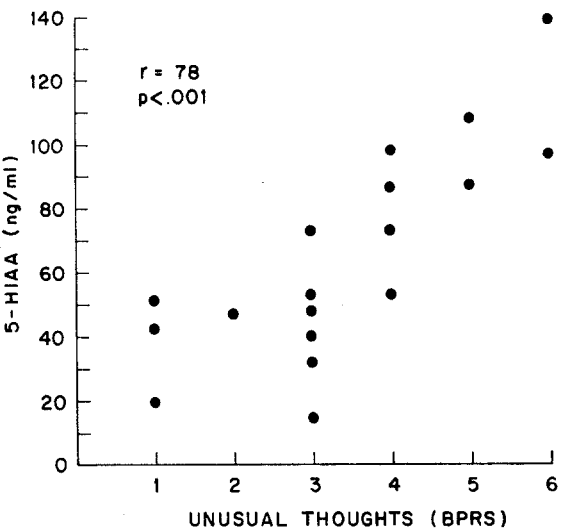

Fig. 2. Lumbar CSF 5HIAA following probeniced vs "unusual thoughts" (BPRS) in acute psychotic patients

prognosis groups. However the Schneider-positive psychotic group had a significantly lower mean Stephens-Astrup score than the Schneider-negative group (19.3 vs. 24.8, $p < 0.001$).

Rimon *et al.* (1971) reported higher pre-treatment baseline HVA values in so-called "paranoid" psychoses. Although in our hands this clinical discrimination is difficult to make, we did compare pre-treatment values for HVA and 5HIAA/HVA between those patients scoring four or more on the BPRS item "suspiciousness" and those patients scoring three or less on this item. We found no differences between the two groups.

Discussion

Two lines of basic neuropharmacological research prompted this study of central 5HT and DA metabolism in psychotic states. First, 5HT metabolism has been implicated in the effects of compounds like D-lysergic acid diethylamide (LSD) (Aghajanian, 1972), and such compounds are known to produce a variety of states which bear a similarity to clinical psychosis. Secondly, the primary chemotherapeutic agents for the treatment of psychotic disorders are known to have profound effects upon DA metabolism (Anden *et al.*, 1964; O'Keefe *et al.*, 1970). It thus seemed reasonable to see whether clinical measurements of 5HT and DA metabolism showed any relationship to clinical parameters in psychotic disorders. The clinical parameters we chose were behavioral ratings (BPRS), prognostic ratings (Stephens-Astrup), and a clinical classification according to certain "nuclear" symptoms (Schneider first rank symptoms). Some of the problems in the interpretation of CSF acid monoamine metabolite values have been discussed (Bowers, 1972a). They include the problem of a variable probenecid effect and the question of the neural populations and processes reflected in lumbar CSF 5HIAA and HVA values. Bearing in mind these limitations, the current findings are of interest. In the present report we find preliminary evidence that psychotic reactions with different symptom profiles have different metabolite patterns. Thus prior to treatment those patients demonstrating the first rank symptoms of Schneider tended to have higher values for 5HIAA relative to HVA as compared to Schneider-negative psychotic patients and two control groups The Schneider-negative group had significantly lower values for 5HIAA relative to HVA compared to the Schneider-positive psychotic group and to the inmate controls. The HVA value for this group was almost significantly higher than that for the Schneider-positive group. However a differential probenecid effect cannot be absolutely excluded and CSF probenecid levels would aid in the interpretation of our findings (Korf and Van Praag, 1971). Thus, we cannot finally determine from our present data whether 5HT turnover is increased or DA turnover decreased in the Schneider-positive group nor whether 5HT turnover is decreased or DA turnover increased in the Schneider-negative group. The latter possibility in the Schneider-negative group would agree with the findings of Rimon *et al.* (1971) who reported higher baseline HVA values (without probenecid) in "paranoid psychotics", a group often considered to have a better prognosis. We have studied a group of patients with psychedelic drug-induced psychoses and found lower 5HIAA/HVA ratios in this group compared to a non drug-induced group. However, in this drug-induced group (who also scored more favorably on prognostic items) the lower ratio seemed to be clearly

due to a decrease in 5HIAA formation since 5HIAA values were significantly decreased (Bowers, 1972c).

It is conceiveable that the trend toward higher HVA values in our current Schneider-negative group could reflect increased activity in this group. Van Praag (1971) feels that CSF HVA reflects primarily motor activity in depressives and we have mentioned the elevated CSF HVA values we previously obtained in a group of agitated depressives. However the Schneider-positive and negative groups in the present study did not differ before treatment on the BPRS, item *motor retardation*. A definitive answer to the question of activity and CSF HVA must await the use of more quantitative measures of activity (Kupfer *et al.*, 1972).

The pre-treatment correlations between 5HIAA and BPRS items related to psychotic disorganization of mental content are of interest. Since "thought disorder" is considered to be a differential feature in some forms of schizophrenia, the high correlation between 5HIAA and "unusual thoughts" on the BPRS deserves further attention. That the present 5HIAA correlations with the BPRS items are not due to a nonspecific effect of anxiety or agitation is supported by our findings in agitated derpessives where CSF 5HIAA was not correlated with agitation (Bowers, 1972b).

Because of the unique effect of antipsychotic compounds upon DA metabolism, we had hoped to find definite pre-treatment correlation between HVA and clinical ratings. However, except for the possible differential values for 5HIAA/HVA in the Schneider-positive and negative group mentioned above, we were unable to show such an interrelationship with the other clinical ratings, including the BPRS item scores.

Our data clearly show that clinical doses of antipsychotic drugs produce an increase in HVA formation in lumbar CSF. Similar results have previously been reported using baseline HVA values in CSF (Persson and Roos, 1969; Bowers *et al.*, 1969) and urine (Bruno and Allegranza, 1965). Previous investigators have tended to conclude that these effects on HVA were related to drug dose or the presence or absence of certain extrapyramidal side effects (Bruno and Allegranzo, 1965; Chase *et al.*, 1970). However, we were not able to find significant correlations between antipsychotic drug dose and HVA response. None of our patients showed clinically-significant extrapyramidal symptoms at the time of the second CSF sampling. The possibility thus remains that some clinical parameters are more precisely related to increases in HVA following antipsychotic compounds. We did not completely test this possibility since all patients were essentially in clinical remission at the time of the second CSF sampling. Our finding that clinical doses of benztropine sufficient to control extrapyramidal symptoms did not correlate with the HVA increase are in contrast to our findings in animals where higher doses of

antiparkinson drugs regularly attenuated the HVA increase following chlorpromazine (Bowers and Roth, 1972). It thus seems unlikely that the clinical effect of antiparkinson drugs in psychotic patients treated with antipsychotic drugs is related to their ability (in high doses) to antagonize in animals the increase in dopamine turnover produced by antipsychotic drugs.

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