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Serum Homovanillic Acid Levels in Schizophrenic Patients and Normal Control Subjects

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Abstract. Schizophrenic patients with an early age at onset of illness had low baseline levels of homovanillic acid (HVA) in serum compared with schizophrenic patients with a late age at onset. After adjustments were made for age at onset, there was a significant partial correlation between positive symptoms and serum HVA. The relationship between positive symptom scores and serum HVA was shifted to the left in the early onset patients, suggesting a relatively increased sensitivity of dopamine-associated response. Patients with severe negative symptoms also had an earlier age at onset and a trend toward lower serum HVA. This study found no difference between mean serum HVA values in schizophrenic patients and normal control subjects.

Key Words. Age at onset, positive symptoms, negative symptoms, dopamine.

Homovanillic acid (HVA) is the major metabolic product of dopamine that is released from the brain into the circulation (Kopin, 1985). It has been proposed that plasma HVA concentrations may provide an index of central dopamine metabolism (Roth and Bacopoulos, 1979), since experimental conditions in animals, such as electrical stimulation or lesions of dopamine pathways and the administration of dopamine agonists or antagonists, produce changes in plasma HVA concentrations that parallel changes in brain HVA levels (Bacopoulos et al., 1979; Kendler et al., 1982).

The finding that treatment-related decreases in plasma HVA concentrations over time are associated with improvement in schizophrenic symptoms (Bowers et al., 1984; Pickar et al., 1986; Chang et al., 1988; Davila et al., 1988; Sharma et al., 1989) has led to the proposal that plasma HVA may be a neurochemical marker of psychosis (Pickar et al., 1986). Some studies have shown significant positive correlations between plasma HVA levels and ratings of total severity of symptoms (Davis et al., 1985; Pickar et al., 1986, 1990; Davidson and Davis, 1988), but other studies have not replicated this finding (Kirch et al., 1988; Maas et al., 1988; Van

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Putten et al., 1989; Javaid et al., 1990; Markianos et al., 1992; Wei et al., 1992). Some studies (Pickar et al., 1984; Doran et al., 1985) but not all (Davidson and Davis, 1988; Baker et al., 1990; Markianos et al., 1992; Wei et al., 1992) have shown significantly higher plasma HVA levels in schizophrenic patients than in normal control subjects. One study found lower plasma HVA levels in treatment-resistant patients with severe negative symptoms compared with normal control subjects (Davidson and Davis, 1988). Other studies of the relationship between plasma HVA and negative or positive symptoms of schizophrenia have also yielded mixed results (Van Putten et al., 1989; Javaid et al., 1990; Pickar et al., 1990).

Because of the conflicting findings in studies of the relationship between symptom severity and plasma HVA, closer attention to possible confounding variables would appear to be indicated. It has been suggested that background variables such as age and sex should be taken into consideration as possible confounding factors in research on psychiatric symptom patterns (Pokorny and Overall, 1970). In particular, the age at first onset of schizophrenic illness is a candidate as a possible confounding factor, since an early age at onset of illness has been associated with increased negative symptoms (Tsuang and Winokur, 1974; Farmer et al., 1983; Johnstone et al., 1989), poor long-term course (Fenton and McGlashan, 1991; Gmur, 1991), and evidence of structural brain abnormalities (Crow et al., 1989; Johnstone et al., 1989; DeLisi, 1992). In addition, post-mortem studies have suggested that chronic presynaptic dopaminergic underactivity is more pronounced in schizophrenic patients whose onset of illness occurred before age 25 (Mackay, 1980). Since severe negative symptoms and poor outcome (Bowers, 1974; van Kammen et al., 1983; Lindström, 1985; Karoum et al., 1987; Davidson and Davis, 1988), as well as structural and functional brain abnormalities (Nybäck et al., 1983; van Kammen et al., 1983; Houston et al., 1986; Losonczy et al., 1986; Doran et al., 1987; Weinberger et al., 1988) have all been linked to low HVA in body fluids, we hypothesized that schizophrenic patients with an early age at onset would manifest relatively lower serum HVA levels.

The present study compares the serum HVA levels (sHVA) in 18 neuroleptic-free schizophrenic patients and 17 normal control subjects. This study examines the relationship between sHVA and positive and negative symptoms while taking into consideration the possible influence of age at onset of schizophrenic illness.

Methods

Subjects. Eighteen neuroleptic-free patients who met *DSM-III-R* criteria (American Psychiatric Association, 1987) for schizophrenia, who gave written informed consent for participation, and who could be managed without medication during the baseline studies were entered into the study. The *DSM-III-R* diagnosis was established using the Structured Clinical Interview for *DSM-III-R* Patient Version (SCID-P; Spitzer et al., 1987b). Patients who had *DSM-III-R* diagnoses of major affective disorder, schizoaffective disorder, or organic mental disorders were excluded from the study. Schizophrenic patients who met *DSM-III-R* criteria for alcohol or substance abuse during the 6 months before admission were excluded from the study. There were no confounding medical problems that would require medication which might interfere with sHVA levels. Because of the low frequency of female veteran admissions to the Dallas Veterans Affairs Medical Center, this study included only male subjects.

Seventeen normal male control subjects were recruited by advertisements at the medical center. Seven of the control subjects had occupations at the level of lesser professional or semi-professional, nine at the level of technician/clerical or skilled workers, and two at the level of unskilled worker (Hollingshead and Redlich [1958] employment level: mean = 3.7, SD = 1.6). Each control also gave written informed consent. The Structured Clinical Interview for *DSM-III-R* Non-Patient Version (SCID-NP; Spitzer et al., 1987a) was conducted with each control subject. Any person with a personal or family history of present or past psychiatric disorder or drug or alcohol abuse was excluded from the control group. For both patients and control subjects, urine drug screens and alcohol saliva tests were obtained before the onset of the study, and subjects whose fluids revealed alcohol or drug use were excluded. Physical examinations were normal for each control subject.

Behavioral Rating Scales. The Brief Psychiatric Rating Scale with anchor points (BPRS-A; Woerner et al., 1988) was performed on all schizophrenic subjects at the end of the medication-free baseline period. To measure negative symptoms, we used the Withdrawal-Retardation factor from the BPRS (Overall and Gorham, 1976), consisting of the items Emotional Withdrawal, Motor Retardation, and Blunted Affect. As our measurement of positive symptoms, we used the sum of the BPRS item scores for Unusual Thought Content, Conceptual Disorganization, Hallucinatory Behavior, Excitement, Grandiosity, Suspiciousness, and Hostility. These seven items were included because of their correspondence to the similar seven items that make up the Positive Scale from the Positive and Negative Syndrome Scale (PANSS; Kay, 1991).

Serum HVA Levels. Seven schizophrenic patients in this study had never been exposed to any neuroleptic treatment before the collection of sHVA samples. All of the remaining 11 patients, who had a history of previous exposure to neuroleptics, had self-discontinued using their neuroleptic medication as outpatients (mean = 208 days before hospitalization). Each patient's history of not taking neuroleptic medications was checked whenever possible with outside sources such as family members and clinic records. On the inpatient unit, each patient's neuroleptic-free status was continued for an additional period (mean = 18 days) before sHVA samples were obtained during which period no psychotropic medications were taken except lorazepam or chloral hydrate in some cases. For all subjects, the total (outpatient + inpatient) neuroleptic-free period was at least 75 days. None of the patients had a history of depot neuroleptic injections within the 6 months before sHVA samples were obtained.

For both control subjects and patients, sHVA was determined as the mean of one to three serum samples that were obtained on separate days during the same week. In the schizophrenic group, 22% of the patients had three samples, 33% had two samples, and 45% had one sample. In the normal control group, 29% of the subjects had three samples, 18% had two samples, and 53% had one sample. The mean coefficient of variation of sHVA between samples was 19.6% for the schizophrenic group and 15.5% for the control group. Samples were obtained between 7:00 and 7:30 a.m. after a 14-hour overnight fast and after 1 hour of restricted activity that was limited to no more than light ambulation. All subjects were on a low monoamine diet (Mussettola et al., 1977; Sharpless, 1977; Kendler et al., 1983) that started at least 3 days before the first sample was collected and continued until all samples were obtained.

Blood samples were centrifuged within 30 minutes after collection. Serum was frozen at -70 °C until analysis. HVA was determined in serum by high performance liquid chromatography (HPLC) with a modification of the method of Chang et al. (1983). The serum sample was treated with hydrochloric acid and the HVA separated from the interfering serum components by liquid/solid extraction on a reverse phase C-18 cartridge. HVA was quantitated by electrochemical detection with a reverse phase C-18 radial compression HPLC column. The sensitivity of the method is < 20 pg per injection and the assay is linear from 1 ng/ml to 30 ng/ml. The intra-assay and the interassay coefficients of variation in our laboratory are < 5%. In assessing this method, we determined that serum was a more appropriate matrix for analysis of HVA since it yielded fewer interfering peaks than plasma

and was more time efficient, and since studies of matched patient specimens yielded equivalent results: HVA determined in split plasma-serum samples yielded a mean concentration of 9.2 ng HVA/ml plasma compared with a mean of 10.5 ng HVA/ml serum ($n = 42$). The Spearman correlation coefficient between the HVA concentrations in the plasma and serum split samples was 0.793 ($p = 0.0001$).

Data Analysis. All statistics were analyzed with SAS Release 6.03 Edition (SAS Institute, Inc., 1988). All statistical analyses in this study used two-tailed probability levels. The mean sHVA values and demographic variables were compared between diagnostic groups by Student's t tests. For the stepwise regression of sHVA, the hypothesized behavioral ratings (total BPRS score, positive symptom score, and negative symptom score) as well as the basic demographic variables (age, educational level, age at first onset of illness, duration of total illness, duration of current episode, and number of episodes) were entered into the analysis. The SAS stepwise regression procedure was used in which variables are added one by one to the model and the F statistic for each variable must be significant at the 0.1500 significance level for entry into the model (SAS Institute, Inc., 1988). After each step, any variable in the model that does not meet the 0.1500 significance level is deleted. Correlations were calculated using the Spearman correlation coefficient to minimize the influence of extreme values. Analysis of covariance was computed using the General Linear Models procedure.

Results

Table 1 shows the demographic and baseline data for the two groups in the study. There was no significant difference in mean age between the schizophrenic patients and the normal control subjects ($t = 0.335$, $df = 33$, $p = 0.740$). The mean educational level was 2 years greater for the normal control group compared with the schizophrenic group ($t = 3.428$, $df = 33$, $p = 0.002$). Mean baseline sHVA did not differ significantly between the schizophrenic patients and the normal control subjects ($t = 0.388$, $df = 33$, $p = 0.701$). Level of sHVA in patients who had no history of neuroleptic treatment (mean = 10.2, SD = 3.7 ng/ml, $n = 7$) did not differ significantly from levels in normal control subjects (mean = 10.3, SD = 2.8 ng/ml, $n = 17$) and patients who had a history of neuroleptic treatment (mean = 10.9, SD = 2.3 ng/ml, $n = 11$; $F = 0.19$; $df = 2, 32$; $p = 0.830$).

Table 1. Baseline data for normal control subjects and schizophrenic patients

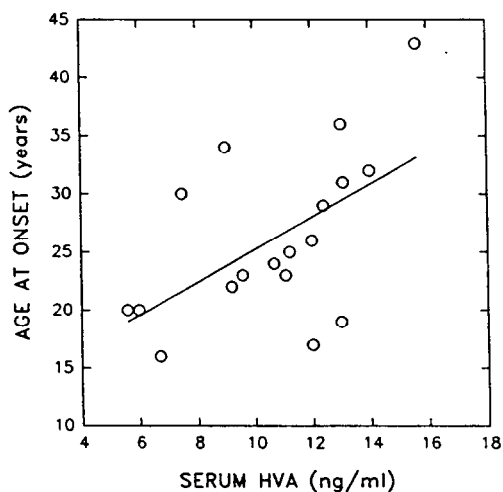
	Normal control subjects ($n = 17$)			Schizophrenic patients ($n = 18$)		
	Range	Mean	SD	Range	Mean	SD
Age (yr)	22-43	32.9	6.4	20-44	33.6	5.5
Education (yr)	12-16	14.3	1.8	8-15	12.3	1.6
Serum HVA (ng/ml)	6.8-16.7	10.3	2.8	5.6-15.6	10.6	2.9
Age at first onset of illness (yr)				16-43	26.1	7.2
Duration of illness (yr)				0-17	7.4	5.9
Duration of current episode (mo)				0.25-60	10.9	13.6
Number of episodes				1-10	4.7	3.7
BPRS score				35-67	49.8	9.1
Positive symptom score				13-38	24.3	6.9
Negative symptom score				3-15	6.8	2.8

Note. HVA = homovanillic acid. BPRS – Brief Psychiatric Rating Scale.

Stepwise multiple regression showed that the “age at first onset of illness” and the “positive symptom score” were the major determinants of sHVA, together accounting for 55% of the variance in sHVA ($F = 9.11$; $df = 2, 15$; $p = 0.003$). Age at first onset contributed 31% of the variance in sHVA ($F = 14.30$; $df = 1, 15$; $p = 0.002$), and positive symptoms contributed 23% of the variance in sHVA ($F = 7.77$; $df = 1, 15$; $p = 0.014$). None of the other factors (age, education, duration of current episode, number of episodes, duration of total illness, total BPRS score, and negative symptom score) contributed significantly to the variance ($p > 0.286$ for each factor).

Fig. 1 shows a plot of sHVA versus age at first onset of schizophrenic symptoms.

Fig. 1. Age at first onset of psychotic symptoms vs. serum homovanillic acid (HVA)



The least squares line was determined by regression analysis.

Patients who had a younger age at first onset tended to have lower values of sHVA ($r = 0.532$, $p = 0.023$). We used a median split to separate the schizophrenic patients into two groups: “early” onset (age at onset < 25 years) and “late” onset (age at onset ≥ 25 years). The mean sHVA was significantly lower in the early onset group compared with the late onset group (Table 2). The total duration of illness was significantly greater for the early onset patients, but the correlation between duration of illness and sHVA was not significant ($r = -0.213$, $p = 0.396$). Table 2 also shows the baseline behavioral rating scores for the schizophrenic patients.

Table 3 shows the correlations between the baseline behavioral rating scores and sHVA for the schizophrenic patients. The simple correlation between the positive symptom scores and sHVA was 0.418 ($p = 0.084$). The partial correlation between the positive symptom scores and sHVA was significant ($r = 0.632$, $p = 0.006$), however, after adjustments were made for age at first onset of schizophrenic symptoms.

Table 2. Baseline data for early and late onset schizophrenic patients

	Early onset (<i>n</i> = 9)			Late onset (<i>n</i> = 9)		
	Range	Mean	SD	Range	Mean	SD
Age (yr)	20-37	31.9	5.1	26-44	35.2	5.6
Education (yr)	10-15	12.3	1.4	8-14	12.3	1.9
Serum HVA (ng/ml)	5.6-13.0	9.3 ¹	2.7	7.5-15.6	12.0	2.5
Age at first onset of illness (yr)	16-24	20.4 ²	2.8	25-43	31.8	5.5
Duration of total illness (yr)	4-17	11.4 ²	4.4	0-12	3.4	4.4
Duration of current episode (mo)	0.25-14.0	7.0	5.4	3-60	14.8	18.1
Number of episodes	2-10	6.2	3.8	1-10	3.2	3.2
BPRS score	42-67	53.8	8.2	35-60	45.8	8.6
Positive symptom score	21-38	26.9	5.7	13-33	21.7	7.3
Negative symptom score	4-9	6.6	1.5	3-15	7.1	3.9

Note. HVA = homovanillic acid. BPRS = Brief Psychiatric Rating Scale.

1. $p < 0.05$, Student's 2-tailed *t* test.

2. $p < 0.01$, Student's 2-tailed *t* test.

Table 3. Spearman correlations between baseline behavioral rating scales and sHVA in schizophrenic patients

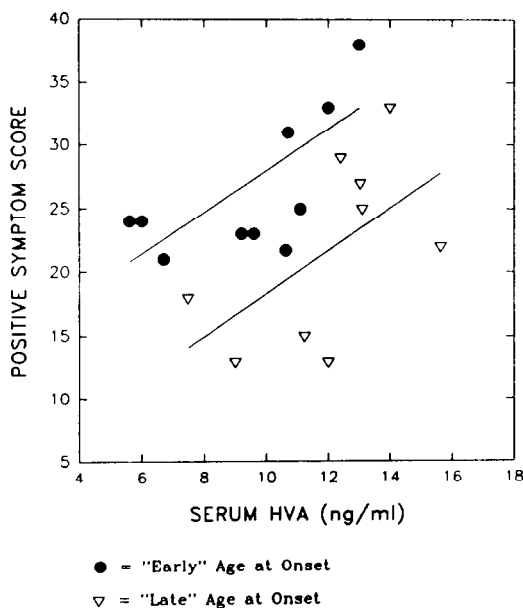
	Simple correlation with sHVA		Partial correlations with sHVA (after adjusting for age at first onset)	
	r_s	p	r_s	p
Positive symptoms	0.418	0.084	0.632	0.006
Negative symptoms	-0.505	0.032	-0.435	0.081
Total BPRS score	-0.075	0.767	-0.200	0.441

Note. sHVA = serum homovanillic acid. BPRS = Brief Psychiatric Rating Scale.

Fig. 2 shows the scattergrams of sHVA vs. positive symptom score for both the early and late age at onset groups. The correlation between sHVA and positive symptom score was 0.722 ($p = 0.015$) for the early onset group versus 0.636 ($p = 0.066$) for the late onset group. For the early onset patients, the regression line of positive symptoms on sHVA was shifted to the left of that found for the late onset group (Fig. 2). This shift to the left was statistically significant as shown by a significant main effect of age at onset ($F = 12.23$; $df = 1, 17$; $p = 0.003$) determined by analysis of covariance of the positive symptom scores with sHVA as the covariate.

There was no significant difference between negative symptom scores in the early and late onset groups (Table 2). However, the schizophrenic patients who had more severe negative symptom scores (negative symptom score > 6.5 , $n = 9$) had a significantly earlier age at onset compared with the patients with less severe negative symptoms (negative symptom score < 6.5 , $n = 9$; more severe negative symptom group: mean = 22.8, SD = 5.0; less severe negative symptom group: mean = 29.4, SD = 7.7 years, $t = 2.17$, $df = 16$, $p = 0.045$). In addition, the patients with severe negative symptoms had lower sHVA levels than the other patients (9.2 vs. 12.1 ng/ml, $t = 2.50$, $df = 16$, $p = 0.024$).

Fig. 2. Positive symptom score vs. serum homovanillic acid (HVA) for both early and late age at onset schizophrenic groups



The least squares lines were determined by regression analysis for each group.

The data initially yielded a significant inverse correlation between the negative symptom scores and sHVA ($r = -0.505$, $p = 0.032$). After adjustments were made for age at onset of illness, the magnitude of the partial correlation between the negative symptom scores and sHVA was reduced to -0.435 ($p = 0.081$) (Table 3). There was no significant correlation between sHVA and total BPRS scores either before or after adjustments were made for age at first onset. There was a trend for an inverse association between positive and negative symptoms ($r = -0.424$, $p = 0.079$) which became significant after adjustment for age at onset ($r = -0.513$, $p = 0.035$).

Discussion

The present study found a significant positive correlation between sHVA and positive symptoms after adjustment for the effects of age at first onset. Among the studies that specifically reported the relationship between positive symptoms and plasma HVA levels, one study (Pickar et al., 1990) reported a significant relationship, but other studies did not (Van Putten et al., 1989; Javaid et al., 1990). It is noteworthy that the study that found a significant relationship between plasma HVA levels and positive symptoms essentially controlled for age at onset by examining a group of schizophrenic patients characterized by "early" onset of illness (mean age at onset = 18.1, SD = 4.1 years) (Pickar et al., 1990).

Several studies have reported the absence of a significant correlation between negative symptom scores and plasma HVA levels (Pickar et al., 1986, 1990; Van

Putten et al., 1989). The present study found a significant inverse correlation between negative symptoms and sHVA before adjustments were made for age at onset, but this finding was confounded by the fact that the patients with severe negative symptoms had a significantly earlier age at first onset of illness. After adjustments were made for age at onset, the significance of the correlation between sHVA and negative symptoms was decreased to the trend level. Davidson and Davis (1988) reported that a group of treatment-resistant chronic schizophrenic patients who were characterized by severe negative symptoms (Keefe et al., 1987) had lower plasma HVA levels compared with normal control subjects. In addition, urinary HVA excretion has been reported to be lower in chronic treatment-resistant schizophrenic patients compared with normal control subjects (Karoum et al., 1987). Several studies have also suggested that low cerebrospinal fluid HVA levels are related to defect symptoms and poor prognosis in schizophrenic patients (Bowers, 1974; van Kammen et al., 1983, 1986; Lindström, 1985). These findings are consistent with the hypothesis that negative symptoms in schizophrenia are associated with chronic presynaptic dopaminergic underactivity (Mackay, 1980).

The present study, after correcting for age of onset, found a trend toward lower sHVA in patients with severe negative symptoms and significantly higher sHVA in patients with severe positive symptoms. Van Kammen et al. (1986) reported that cerebrospinal fluid HVA concentrations showed both a significant negative correlation with negative symptoms and a positive correlation with thought disturbance. Davidson and Davis (1988) reported low plasma HVA levels in patients with severe negative symptoms, in addition to a significant positive correlation between plasma HVA levels and severity of psychosis. It has been suggested (Weinberger, 1987; Davidson and Davis, 1988; Davis et al., 1991; Grace, 1991; Deutch, 1992) that these findings could be accounted for by the simultaneous occurrence of hypodopaminergia in prefrontal neurons (related to negative symptoms) and hyperdopaminergia in mesolimbic neurons (related to positive symptoms). The simultaneous occurrence of hypodopaminergia in the prefrontal cortex and hyperdopaminergia in mesolimbic neurons has been shown to be possible in animal experiments in which the destruction of dopaminergic nerve terminals in rat prefrontal cortex resulted in increased dopamine turnover in nucleus accumbens (Pycock et al., 1979).

The present study found that schizophrenic patients with an earlier age at onset of illness had low sHVA compared with patients with a later age at onset. This result is consistent with post-mortem findings (Mackay, 1980) which suggested that decreases in presynaptic dopaminergic turnover were more pronounced in early onset schizophrenic patients (< 25 years old). In the present study, the relationship between positive symptom scores and sHVA was shifted to the left for the early onset patients, suggesting a relatively increased sensitivity of dopamine-mediated response in the early onset patients. These findings are consistent with a model in which chronically diminished dopamine turnover (associated with low sHVA levels in the early age at onset group) causes supersensitivity of postsynaptic dopamine receptors or other homeostatic changes that result in an abnormally augmented transient dopamine response to stimuli, leading to increased positive symptoms (Mackay, 1980; Heritch, 1990; Grace, 1991; Deutch, 1992).

In the present study, patients with severe negative symptoms had a significantly earlier age at onset. Early onset of illness has been associated with blunted affect and poor premorbid adjustment (Tsuang and Winokur, 1974; Farmer et al., 1983) as well as poor long-term course (Fenton and McGlashan, 1991; Gmur, 1991). Schizophrenic patients whose initial episode of illness was characterized by predominantly negative symptoms had a lower age at onset compared with positive or mixed syndrome patients (Rohde et al., 1991). In another study, early onset schizophrenic patients (< 25 years of age for men and 28 for women) manifested increased negative symptoms as well as a significant association between psychological impairment and reduced brain area (Johnstone et al., 1989). In addition, early onset schizophrenic patients have been reported to have reductions in the relative width of left temporal and occipital brain regions (Crow et al., 1989) or greater ventricular enlargement (DeLisi, 1992).

It has been suggested that early age at onset may reflect a defective brain developmental process that may be related to structural brain abnormalities seen in adult schizophrenic patients (Crow, 1991; DeLisi, 1992). It has also been suggested that impaired brain development during fetal and neonatal life may result in the negative syndrome (Foerster et al., 1991). It is tempting to speculate that a similar developmental brain abnormality may be associated with chronic presynaptic dopaminergic underactivity, as reflected by the low concentrations of HVA found in the body fluids of patients characterized by early age at onset of illness and negative symptoms.

The present study did not find a significant correlation between sHVA and total BPRS scores either before or after adjustments were made for the effects of age at onset. Several studies also have reported the absence of a significant relationship between plasma HVA levels and total BPRS scores or global ratings of severity of illness (Kirch et al., 1988; Maas et al., 1988; Van Putten et al., 1989; Javaid et al., 1990; Markianos et al., 1992; Wei et al., 1992). However, other studies have shown significant positive correlations between plasma HVA levels and total BPRS scores or global ratings of severity (Davis et al., 1985; Pickar et al., 1986, 1990; Davidson and Davis, 1988).

Since both negative symptoms and positive symptoms might correlate with sHVA, differences in the relative proportions of negative and positive symptoms in the patients within each study might account for the differences in the findings reported in the literature. On the other hand, Davis et al. (1991) have suggested that mean values of plasma HVA concentrations that are determined on the basis of multiple samples for each subject are more likely to yield significant correlations with ratings of symptom severity. In the current study, only 55% of the patients had more than one sample drawn for sHVA determination.

This study found no significant difference in sHVA between normal control subjects and schizophrenic patients. Similar findings have been reported by Baker et al. (1990), Markianos et al. (1992), and Wei et al. (1992). The results of the present study seem unlikely to have been influenced by the duration of neuroleptic washout (minimum neuroleptic-free period = 75 days) since sHVA levels in patients who never had been exposed to neuroleptics did not differ significantly from those in patients who

had a history of previous neuroleptic treatment. Some studies (Pickar et al., 1984; Doran et al., 1985) have shown higher plasma HVA levels in schizophrenic patients compared with control subjects. On the other hand, Davidson and Davis (1988) reported lower plasma HVA levels in treatment-resistant chronic schizophrenic patients compared with normal control subjects (Davidson and Davis, 1988). None of these studies controlled for the age at first onset of schizophrenia. Since the present study suggests that age at first onset may contribute significantly to the variance (31%) in sHVA, it is possible that the discrepancies reported in the literature may have resulted from differences in the age at first onset in the schizophrenic subjects studied.

It is somewhat surprising that the early onset patients in the present study may have had an apparently shorter mean duration of current episode than late onset patients; however, the difference was not statistically significant ($p > 0.24$). Because of the small number of subjects in each group, the results of this study should be regarded as preliminary. A cautious interpretation is also indicated because the proportion of plasma HVA that originates from brain may be as low as 12-24% (Kopin et al., 1988; Lambert et al., 1991). One should be especially cautious about interpreting presynaptic and postsynaptic brain activity from measurements of sHVA, and any such interpretations should be regarded as speculative at present. Furthermore, lorazepam or chloral hydrate was allowed to be taken during the baseline period in some cases. It has been reported that benzodiazepines may lower brain HVA concentrations in animals (Wood, 1982; Singhal et al., 1983; Bowers et al., 1991). In normal human subjects, however, the benzodiazepine drug alprazolam had no effect on plasma HVA (Zemishlany et al., 1991).

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