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Plasma Homovanillic Acid Concentration and the Severity of Schizophrenic Illness

Abstract. *Concentrations of plasma homovanillic acid before treatment were highly correlated with global severity of illness in schizophrenic patients, both before and after treatment. In contrast, a fixed dose of haloperidol did not affect those concentrations. Thus, in patients with a diagnosis of schizophrenia, plasma homovanillic acid may reflect the severity of illness, but not be influenced by short-term pharmacological perturbations by neuroleptics.*

Plasma homovanillic acid (pHVA) of rodents and subhuman primates can reflect brain turnover of dopamine (*1, 2*). For example, neuroleptic-induced elevations in brain dopamine metabolism are reflected in changes in pHVA concentration (*3*). These and other results have led to the conclusion that about 50 percent of pHVA derives from the brain (*4*). Furthermore, pHVA may better reflect cortical dopaminergic activity than does cerebrospinal fluid (CSF) HVA concentration (*5*). Taken together, these data have encouraged the study of pHVA in humans.

Preliminary investigations of pHVA concentration have produced inconsistent results. Although pHVA concentration was decreased by the dopamine agonist apomorphine (*6*), a neuroleptic effect on pHVA concentration has not been shown. However, numerous methodological difficulties can influence the measurement of pHVA concentration. Activity and diet are likely to affect pHVA concentrations (*7*), and circadian rhythms are likely. Thus, human studies must control these factors to maximize whatever clinical utility pHVA concentration might have.

Dopaminergic mechanisms have been thought to play a role in the schizophrenias, primarily because neuroleptic agents all decrease dopaminergic neurotransmission (*8*). Conversely, drugs that enhance central dopaminergic activity can worsen schizophrenic symptoms (*9*). However, not all schizophrenics are benefited by neuroleptic treatment, nor are all worsened by dopaminergic agonists (*10*). More direct evidence for a dopaminergic abnormality in schizophrenia is lacking. To the extent that pHVA concentration reflects central dopaminergic mechanisms, pHVA can provide insight into the importance of dopamine in schizophrenia. We now report a positive relation between the severity of schizophrenic symptoms and concentrations of pHVA in drug-free patients.

Participating in the study were 18 schizophrenic males (mean age, 41 years) meeting Feighner or Research Diagnostic Criteria after a structured interview (*11*). All patients were on a standard low monoamine diet and free of any neuroleptics for a minimum of 4 weeks.

The study consisted of 29 consecutive days of haloperidol administration. On day 1 an indwelling catheter was inserted at 0830, and baseline samples for pHVA were drawn at 0930, 1000, 1030, and 1050. All patients were at complete bed rest for 12 hours before the study and had been fasting except for water for 14 hours. At 1100, haloperidol (0.2 mg/kg) was injected intramuscularly; beginning at 1110, seven additional samples for pHVA were drawn at hourly intervals (*12*). Thereafter, patients received 10 mg of haloperidol twice daily for 28 days. Assessment of symptom severity was performed on day 1 before the initial haloperidol administration and again on days 22 and 29. The assessment was performed by two independent raters using the Clinical General Impression (CGI) and Brief Psychiatric Rating Scale (BPRS) (*13*).

Haloperidol administration produced a sporadic effect on pHVA in individual patients, but no mean effect in all pa-

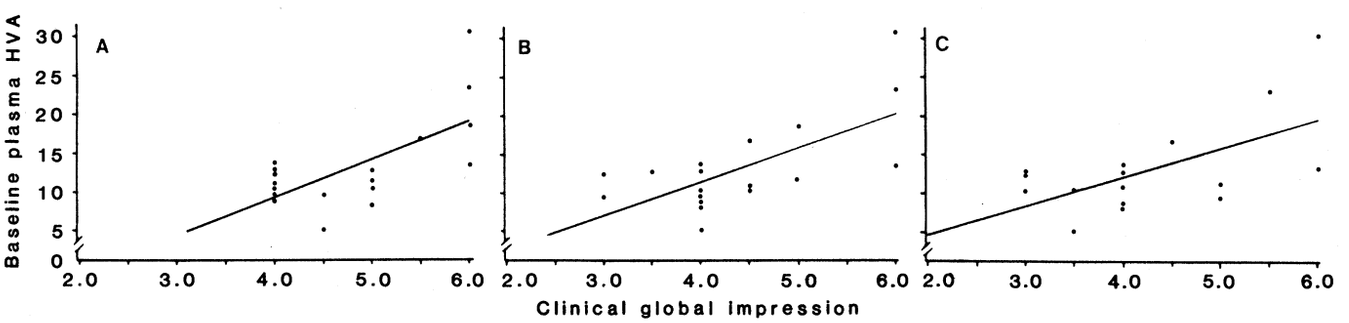

Fig. 1. Correlations between baseline pHVA and the CGI score on (A) day 1 (B) day 22, and (C) day 29.

tients could be demonstrated at any time from 10 minutes to 6 hours after the initial haloperidol injection (*14*). The correlation between the mean value of four pHVA concentrations sampled before haloperidol administration (baseline pHVA) and symptom severity at days 1, 22, and 29 was examined (*15*). pHVA concentrations were significantly correlated with day 1 CGI scores ($r = 0.66 \pm 0.10$, $n = 18$, $P < 0.002$) (*16*). A similar but less robust relationship existed with the total BPRS score ($r = 0.33$). The CGI on days 22 and 29 was also correlated with the baseline pHVA concentrations ($r = 0.67 \pm 0.14$, $n = 18$, $P < 0.002$; $r = 0.61 \pm 0.17$, $n = 16$, $P < 0.011$, respectively) (Fig. 1). Similar trends were found for the BPRS ($r = 0.57$, $P < 0.01$ on day 22; $r = 0.42$, $P < 0.09$) (*17*).

The decrement in CGI or BPRS scores produced by haloperidol treatment after 22 or 29 days was not significantly correlated with baseline pHVA. Thus, baseline pHVA was of little prognostic value.

The relation between baseline pHVA concentration and assessment measurements suggests that those patients with the most severe symptoms of schizophrenia have the highest pHVA concentrations. Such nonspecific factors as diet, activity, and circadian rhythm cannot account for this relation. The correlations between baseline pHVA concentration and symptom severity persists throughout the study, perhaps because baseline severity measures powerfully predict severity after 3 weeks ($r = 0.75$, $P < 0.001$) and 4 weeks ($r = 0.67$, $P < 0.001$) of haloperidol treatment.

Acute neuroleptic-induced perturbations produced in the human nigrostriatum are reflected in increments of CSF HVA, (*18*) but in this study were not demonstrated in pHVA concentrations. Perhaps pHVA does not reflect dopamine turnover in the nigro-striatal area. Instead the high correlation between pHVA and symptom severity suggests that pHVA provides information more closely related to the severity of schizophrenic symptoms than may CSF HVA (*19*). Further studies should elucidate those relationships and the general clinical utility of pHVA measurements (*20*).

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11. Correlation coefficient for independently assigned diagnosis is 0.80 for RDC and 0.91 using Feighner criteria. These inclusion criteria yield a fairly representative sample of male patients diagnosed as schizophrenic by contemporary clinical investigators [J. Overall and L. E. Hollister, *Arch. Gen. Psychiatry* **36**, 1198 (1979)]. The sample was obtained by screening consecutive admissions to the psychiatry service of the Bronx Veterans Administration Medical Center.
12. Plasma samples were assayed for free HVA by gas-chromatographic–mass-spectrometric quantitation (Finnigan 4021 GC/MS) [G. C. Hammer, B. Hornstedt, R. Ryhaye, *Anal. Biochem.* **25**, 532 (1968), G. C. Hammer and Q. Q. Rittesling, *Anal. Chem.* **43**, 298 (1971)].
13. Between the two raters observing the same interview, $r = 0.94$.
14. A spontaneous pHVA downtrend between 0900 and 1200 was observed in a previous study (*7*) suggesting a dopamine-HVA circadian rhythm. It is unlikely that the expected haloperidol-induced increase in mean pHVA was obliterated by this small, spontaneous pHVA downtrend, although this possibility could not be entirely ruled out.
15. Two patients dropped out of the study by day 29, accounting for the different sample size as the study progressed. No particular bias in the data can be ascribed to these dropouts.
16. The Pearson product-moment correlation coefficient was used with the boot-strap method for estimating error. This procedure allows an estimate of the reliability of the observed correlation without the usual assumptions about the normal distribution of sample scores. For each set of N data points, a computer was programmed to generate 1000 sample correlations by sampling N observations with replacement 1000 times. The error reported for each correlation represents the upper and lower bounds around the mean for 68 percent (680) of the computer-generated correlations. Since the bootstrap uses the actual data points and makes no assumptions about the underlying distribution, these confidence limits and associated probability levels are accurate regardless of any apparent outliers [P. Diaconis and B. E. Fron, *Sci. Am.* **3**, 116 (May 1983)].
17. "Positive symptoms" of the BPRS—conceptual disorganization, grandiosity, suspiciousness and unusual thought content—were more highly correlated with baseline pHVA than total BPRS was (day 22, $r = 0.60$, $P < 0.009$; day 29, $r = 0.54$, $P < 0.034$).
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19. The correlation between CSF HVA and symptom severity was examined in patients diagnosed as schizophrenic by the Research Diagnostic Criteria, six of whom are reported in the pHVA study. Patients were all drug-free for at least 2 weeks. Probenecid (100 mg/kg) was administered in divided doses starting the evening before lumbar puncture, which was performed at 1400 after 14 hours of fasting and bed rest. No correlation was found between CSF HVA and symptom severity (CGI).
20. While this work was being prepared for submission we became aware of a similar study on the effect of neuropeptides on pHVA [D. Pickar *et al.*, *Science* **225**, 954 (1984)]. This study reported a time-related neuroleptic-induced reduction in pHVA, which was positively correlated with rating of psychosis and improvement in psychosis. Our study complements those results.
21. Data contained in this paper were presented at the annual meeting of the Society of Biological Psychiatry, Los Angeles, May 1984. Supported by SBRC grant 4125-019 and general medical research grant 4125-021 from the Veterans Administration and NIMH grant MH37922. We thank A. Rothpearl, D. Dunn, V. Brown, N. Sherman, and M. Tzirtzipis for their cooperation in the production of this report.

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