

Differential Effects of Mental Stress on Plasma Homovanillic Acid in Schizophrenia and Normal Controls

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We previously reported that mental stress by Kraepelin's arithmetic test decreases plasma homovanillic acid (pHVA) levels in psychiatrically normal healthy human subjects. The present study was undertaken to determine whether this pattern of changes in pHVA concentrations resulting from mental stress is altered in patients with schizophrenia. Fourteen male patients with schizophrenia including those under ongoing neuroleptic treatment and 14 normal male volunteers participated in the study. Following overnight fast and restricted physical activity, the subjects performed Kraepelin's arithmetic test for 30 minutes. Plasma samples were collected immediately before and after the test for measurement of pHVA levels. A significant diagnosis by Kraepelin's test effect was observed due to a decrease in

pHVA levels by the Kraepelin test in control subjects but not in patients with schizophrenia. Changes in pHVA levels during the Kraepelin test positively correlated with pre-test pHVA levels in control subjects, while this correlation was not observed in patients with schizophrenia. These results may be further support for the presence of a dopamine-dependent restitutive system in the brain. The absence of response of pHVA levels to mental stress in patients with schizophrenia may indicate that the dopamine restitutive system in these patients is disrupted or already down-regulated, as previously predicted.

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The relevance of dopamine (DA) to the pathophysiology of schizophrenia has been extensively documented (e.g., Reynolds 1983; Seeman et al. 1993; Wong et al. 1986). Despite some argument (Kopin et al. 1988; Lambert et al. 1993; Maas et al. 1988), several lines of investi-

gations have focused on plasma levels of homovanillic acid (pHVA), a major metabolite of DA, for the study of DA-related mental disorders such as schizophrenia based on the assumption that dysfunction in central dopaminergic activity is, to some extent, reflected in this peripheral measure (see Friedhoff and Amin 1997 for review). While conflicting results have been reported regarding differences in pHVA levels between patients with schizophrenia and control subjects (Doran et al. 1985; Koreen et al. 1994; Maas et al. 1993; Pickar et al. 1984; Steinberg et al. 1993; Sumiyoshi et al. 1997a; Whelton et al. 1993), there has been accumulated evidence for the association between pHVA levels in schizophrenia and the outcome of neuroleptic treatment (Akiyama et al. 1995; Chang et al. 1993; Davis et al. 1985; Garver et al. 1997; Green et al. 1993; Nagaoka et al. 1997; Sumiyoshi et al. 1997b).

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The presence of a DA-dependent protective system in the brain to maintain mental stability has been proposed (Friedhoff 1985, 1986, 1988). Friedhoff (1988) has hypothesized that a physiological function of the dopaminergic system is to make the brain more resistant to psychotic destabilization by decreasing its own activity in the face of stress, that is reflected in the change of pHVA levels. This hypothesis of the dopaminergic buffer system or the "DA-dependent restitutive system" (Friedhoff 1985, 1986, 1988) may be supported by our recent observation indicating a decrease in pHVA levels during the Kraepelin arithmetic test in psychiatrically normal healthy volunteers (Sumiyoshi et al. 1997c, 1998).

According to the DA-dependent restitutive system theory, the psychotic symptoms of schizophrenia may occur in an individual when (1) there are deficiencies in the function of this system itself which normally down-regulates adequately in the face of psychotogenic factors (environmental, psychological, genetic, or physiological) to prevent developing psychosis, or (2) these precipitating psychotogenic factors are so persistent that even adequate dopaminergic compensation (down-regulation) is overridden (Friedhoff 1986). In the former case, administration of neuroleptic drugs that are DA receptor blockers would down-regulate the system leading to symptomatic improvement (Friedhoff 1986). Therefore, it is speculated that blunted dopaminergic response to stress represented by pHVA levels would be observed in patients with schizophrenia, independent of whether they are neuroleptic-naïve or already receiving neuroleptic treatment, due to a disrupted or already down-regulated DA-dependent restitutive system.

The aim of the present study was to test the hypothesis that the decrease in pHVA levels due to mental stress resulting from the Kraepelin arithmetic test (Sumiyoshi et al. 1997c, 1998) would be blunted in patients with schizophrenia. The study design employed both neuroleptic-naïve patients with schizophrenia and those under ongoing neuroleptic treatment, as it is expected from the above considerations that blunted dopaminergic response to stress would be observed across these patient groups.

SUBJECTS AND METHODS

Fourteen male inpatients with schizophrenia who met DSM-IV criteria for schizophrenia or schizophreniform disorder and 14 male psychiatrically normal healthy volunteers participated in the study. Diagnosis was based on structured interview by experienced psychiatrists and medical history. All subjects gave written consent before entry to the study. Each had a physical and neurological examination, as well as a variety of standard laboratory tests to screen for medical illness. Demographic data of these subjects are presented in Table 1. Seven patients were under ongoing neuroleptic treatment that had started at least 6 months before. These patients received the last neuroleptic administrations 12 h before taking the Kraepelin test. The rest of the patients were neuroleptic-naïve. Physical exercise, high-monoamine diets, alcohol, and caffeine were restricted for all subjects from the entry to the study (>24 h prior to blood sampling).

Table 1. Plasma Homovanillic Acid Levels (ng/ml) before and after Kraepelin's Arithmetic Test

Controls				Schizophrenia				Drug Dose ^a	Duration of Illness
	Age (yr)	Pre-Test	Post-Test		Age (yr)	Pre-Test	Post-Test		
a	20	6.59	5.79	A	16	3.54	3.58	naïve	1.5 yr
b	24	8.08	7.20	B	19	4.87	6.68	naïve	2 mo
c	25	11.38	9.76	C	21	4.65	4.70	naïve	2 yr
d	26	6.61	6.10	D	22	5.84	5.48	6.2	5 yr
e	27	6.99	6.76	E	22	10.76	11.97	naïve	6 mo
f	28	6.55	6.36	F	25	7.76	7.72	18<	7 yr
g	28	7.20	6.93	G	25	7.94	8.05	naïve	1 yr
h	29	6.12	6.32	H	29	5.18	4.82	naïve	13 yr
i	30	6.76	6.86	I	30	6.20	5.19	2	4 yr
j	30	8.24	6.77	J	30	10.78	9.33	naïve	10 mo
k	31	3.89	3.36	K	31	7.69	7.25	9.8	3 yr
l	31	6.14	5.95	L	38	10.37	10.17	5.7	20 yr
m	34	8.78	6.78	M	40	5.23	5.36	8	13 yr
n	34	6.98	6.63	N	51	8.95	10.20	10	25 yr
Mean	28.4	7.16	6.54 ^b		28.5	7.12	7.18		
SE	1.0	0.45	0.35		2.5	0.65	0.67		

^aDrug doses are expressed as haloperidol equivalent (mg/day).

^bSignificantly different from pre-test value ($p < .005$ by two-tailed paired t -test).

The Kraepelin test and blood sampling procedure was adopted from our previous report (Sumiyoshi et al. 1998). Briefly, the subjects underwent the pre-test blood sampling through an intravenous line, that had been obtained at least 30 min before, at 9:00 AM on the day of investigation following an overnight fast. The subjects rested after the venous line was inserted. Immediately after the pre-test blood sampling, the subjects performed a modified version of Kraepelin's arithmetic test (Kuraishi et al. 1957) for 30 min. On termination of the Kraepelin test (30 min after the pre-test blood sampling), blood samples were again collected for measurement of the post-test pHVA levels. Plasma was separated by centrifugation and stored at -80°C until the free HVA was measured.

Plasma HVA analysis was carried out by high-performance liquid chromatography (HPLC) with coulometric detection using d.l.-Isoproterenol as internal standard (Sumiyoshi et al. 1998). The coefficients of variation (CV) for within-day ($n = 6$) and between-day ($n = 6$) analyses of pHVA were 2.4% and 3.3%, respectively.

Repeated measures analysis of variance (ANOVA) were performed to determine the diagnosis (schizophrenia or control subjects) by Kraepelin's test effect between these two groups. Pre- and post-Kraepelin test pHVA levels in each group were compared by two-tailed paired t -test. Spearman's correlation coefficients were obtained relating pre-test pHVA levels with changes in pHVA values (calculated by subtracting post-test pHVA levels from pre-test pHVA levels) in each group. Differences were considered to be significant when p -values were less than .05.

RESULTS

Plasma HVA levels before and after the Kraepelin test in each subject are presented in Table 1. There was no significant correlation between age vs. pre- or post-test pHVA levels both within and across the patient or control groups (data not presented). In subjects with schizophrenia, the pre- or post-test pHVA levels of 7 patients under ongoing neuroleptic treatment did not differ significantly from those of 7 neuroleptic-naïve patients ($F(1,12) = .21$, $p = .65$ and $F(1,12) = .053$, $p = .82$ by ANOVA, respectively). Neuroleptic doses did not correlate significantly with pre- or post-test pHVA levels in 7 patients receiving neuroleptic treatment (data not shown). Repeated measures ANOVA revealed a significant diagnosis by Kraepelin's test effect ($F(1,26) = 5.35$, $p < .03$), accompanied with no significant effect of diagnosis ($F(1,26) = .16$, $p = .70$). In control subjects, a significant decrease in pHVA levels due to the Kraepelin test was observed ($t = 3.54$, $p < .005$), while pHVA levels in patients with schizophrenia were not affected by the Kraepelin test ($t = -.22$, $p = .83$).

Figure 1 demonstrates the relation between pre-test pHVA levels and the value of changes in pHVA levels following the Kraepelin test. Changes in pHVA levels during the Kraepelin test positively correlated with pre-test pHVA levels in control subjects ($r_s = .66$, $p < .02$), while this correlation was not observed in patients with schizophrenia ($r_s = .15$, $p = .58$). The value of changes in pHVA levels following the Kraepelin test did not correlate significantly with age in control subjects, schizophrenic patients, or the combined population (data not shown). No significant difference was found in the value of changes in pHVA levels between neuroleptic-naïve patients and those receiving neuroleptic treatment ($F(1,12) = .38$, $p = .55$). Neuroleptic doses did not correlate with the value of change in pHVA levels following the Kraepelin test in 7 patients receiving neuroleptic treatment (data not shown).

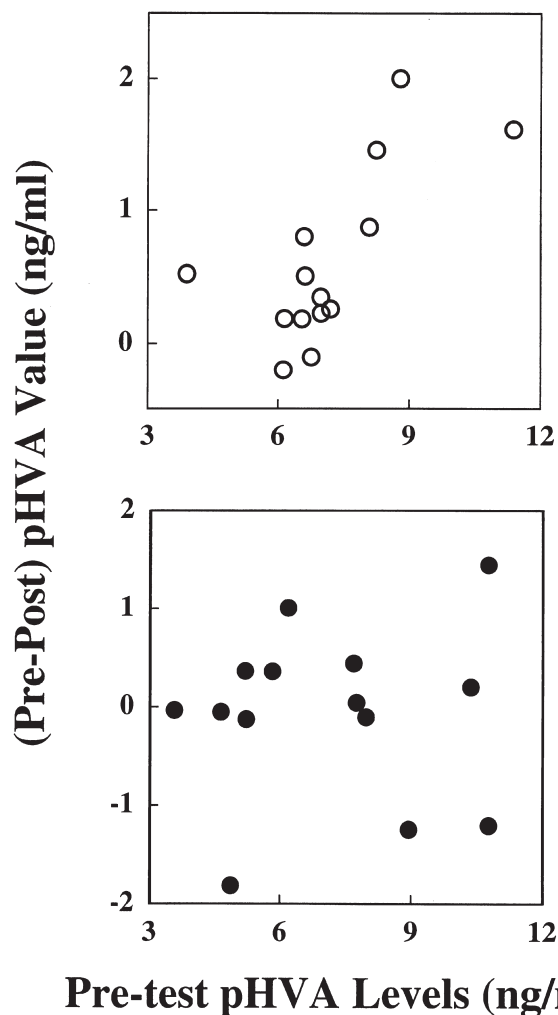


Figure 1. Correlations between the baseline (pre-test) pHVA levels and the value of changes in pHVA levels during the Kraepelin test. Top panel, control subjects; bottom panel, schizophrenic patients.

DISCUSSION

Mental stress resulting from the Kraepelin test produced different change patterns of pHVA levels in patients with schizophrenia and control subjects. While a decrease in pHVA concentrations was observed in control subjects, pHVA levels in patients with schizophrenia were not significantly altered by mental stress (Table 1). Moreover, the value of changes in pHVA concentrations due to mental stress correlated positively with pre-test pHVA levels in control subjects but not in patients with schizophrenia (Figure 1).

The observed decrease in pHVA levels due to mental stress in control subjects may be explained, at least in part, by changes in the central dopaminergic activity (Sumiyoshi et al. 1998). It has been suggested that the DA turnover in subcortical brain regions such as nucleus accumbens constitutes the major component of the brain HVA output (Csernansky et al. 1990; Lambert et al. 1991). It has also been reported that stress causes a reduction in dopaminergic activity in subcortical nuclei via mechanisms involving increased cortical dopaminergic activity (Friedhoff et al. 1995). Thus, it is possible that the decrease in pHVA concentrations during stress in control subjects was associated with decreased dopaminergic activity in the subcortical area such as nucleus accumbens.

The blunted dopaminergic response to mental stress in schizophrenia, as evidenced by the absence of a decrease in pHVA levels, may be further support for the presence of a DA-dependent restitutive system in the brain (Friedhoff 1985, 1986, 1988; Friedhoff et al. 1995). Together with the lack of a correlation between the baseline pHVA levels and the change values in pHVA levels during mental stress in schizophrenia (Figure 1), the results reported here may indicate that the DA-dependent restitutive system, which normally decreases its own activity in the face of stress, may be disrupted or already down-regulated in schizophrenia, as previously predicted (Friedhoff 1985, 1986, 1988). If cortical and subcortical dopaminergic responses to mental stress is associated with the observed change in pHVA levels in control subjects as discussed above, the results in schizophrenia reported here may have relevance to the suggestion that alterations in the function of frontal cortex and limbic areas result in reduced ability to cope with stress leading to decompensation in schizophrenia (Deutch et al. 1990).

The existence of the DA-dependent restitutive system may reconcile the clinical observation that schizophrenic patients who have low pretreatment dopaminergic activity respond poorly to neuroleptic treatment (Chang et al. 1993; Davis et al. 1985; Green et al. 1993; Sumiyoshi et al. 1997b) with the general view that neuroleptic medication exerts its therapeutic effect by decreasing dopaminergic activity (see Friedhoff 1988 for review).

Several studies report the effect of neuroleptic treatment on pHVA levels. For example, an initial increase in pHVA levels followed by a decrease into the baseline levels has been reported in some patients taking typical neuroleptic drugs such as haloperidol within a relatively short period (4–6 weeks) (Davila et al. 1988; Green et al. 1993). In some patients receiving neuroleptics studied here, a part of down-regulation of dopaminergic activity may have been achieved by a long-term (>6 months) neuroleptic treatment. However, there was no evidence for differences in pre- or post-test pHVA levels and the change values in pHVA concentrations during stress between neuroleptic-naïve patients and those under ongoing neuroleptic treatment. Moreover, in the latter group of patients, no significant correlations were found between these measures of pHVA and neuroleptic doses administered. Although the small samples of our groups require caution for any interpretations, these results suggest that the deficient DA-dependent restitutive system reflected by blunted pHVA response is present in patients with schizophrenia whether or not they are receiving neuroleptics. Further studies including a larger number of neuroleptic-naïve subjects combined with psychopathology data would strengthen the clinical significance of the results reported here for the study of schizophrenia.

In conclusion, differential effects of mental stress on pHVA levels between control subjects and patients with schizophrenia were found due to the absence of a decrease in pHVA levels in schizophrenia. The value of changes in pHVA concentrations during stress correlated significantly with pre-test pHVA levels only in control subjects. Although our preliminary study with the small number of subjects limits the conclusions to be drawn, these results may be further support for the presence of a DA-dependent restitutive system in the brain.

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