
Plasma Homovanillic Acid Concentrations in Catatonia

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We investigated the dopamine metabolite plasma homovanillic acid (plasma HVA) levels in 37 catatonic patients on the day of admission before initial medication as well as in 17 healthy controls.

In a prospective study catatonic syndrome was diagnosed according to criteria of Lohr and Wiesniewski (1987) and Rosebush et al (1990) whereas comorbid diagnosis was made by Diagnostic and Statistical Manual of Mental Disorders, 3rd ed, revised (DSM III/R) (APA 1987). On the day of admission blood samples were taken before initial medication. Compared to controls (80.1 ± 40.1 pmol/mL) catatonic patients showed significantly ($p = 0.0286$) increased plasma HVA (140.9 ± 53.6 pmol/mL). Catatonic patients free of neuroleptic medication ($n = 21$) differed significantly ($p = 0.0416$) from controls whereas neuroleptically treated catatonics ($n = 16$) did not.

Our findings of increased plasma HVA in catatonia are explained by an alteration in either mesolimbic or mesocortical dopaminergic function, as is assumed in the case of schizophrenia. As an alternative, it may be due to increased nigrostriatal function, which can lead, as shown in animal experiments with the dopamine agonist amphetamine, to hypokinetic states resembling catatonia in humans.

Key Words: Catatonia, plasma HVA, dopamine

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Introduction

Kahlbaum (1874) introduced the term catatonia to describe patients with a wide range of motor abnormalities including immobility, mutism, posturing, grimacing, rigidity, negativism, staring, stereotypy, verbigerations, waxy flexibility, echolalia, and echopraxia. In contrast to Kahlbaum, Kraepelin (1905) and Bleuler (1911) primarily re-

garded catatonia as a subtype of schizophrenia and, until now, DSM III/R (APA 1987) has continued with such a definition.

However, the more recent literature emphasizes the notion that catatonia should be considered instead as a syndrome associated with different diseases, both organic and nonorganic (Gelenberg 1976; Editorial 1986; Taylor 1990; Fink et al 1993).

The pathophysiology of catatonia is unknown, and its relationship with Parkinson's disease and schizophrenia has never been clarified (Rogers 1985). It displays hypokinetic motor features (akinesia, rigidity, flexibility), more or less similar to Parkinson's disease, in which nigrostri-

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tal dopamine is decreased. Catatonia, however, occurs often in patients with chronic schizophrenia (Lund et al 1991; McKenna et al 1991), in whom mesocortical dopamine seems to be reduced (Davis et al 1991). In addition, catatonia can often be observed in patients with acute schizophrenia (Rosebush et al 1990), in whom mesolimbic dopamine is presumed to be elevated (Chang et al 1990). Hence, dopamine and the balance between its three systems (nigrostriatal, mesolimbic, mesocortical) might be central in the pathophysiology of catatonia. Moreover, catatonia can be associated with affective illnesses; it is still unclear whether these are related to dopaminergic dysfunction (Fink et al 1993).

To investigate dopaminergic function, measurements of the dopamine metabolite homovanillic acid (HVA) in plasma have been among the most widely used strategies for studying the underlying function of central dopamine in neuropsychiatric disorders. This approach is based on the understanding that metabolite production reflects neurotransmitter release and turnover in the brain (Bacopoulos et al 1978; Amin et al 1992). Various findings have led to the interpretation that about 30–50% of plasma HVA (pHVA) is of central origin (Kopin 1978; Bacopoulos et al 1979; Maas et al 1980; Sternberg et al 1983; Kopin 1992).

Studies of plasma HVA in catatonic syndrome are not known to us so far. There was one investigation of urinary dopamine metabolites in periodic catatonia by Gjessing (1974), who found increased urinary HVA and dopamine during the catatonic phase whereas, in the healthy interval, HVA dopamine values did not differ from those in healthy controls.

In the present prospective study we determined plasma HVA levels in 37 catatonic patients before initial medication.

Patients and Methods

We investigated 37 catatonic patients ($n = 37$, 21 women, 16 men), all white and aged between 18 and 55 years (33.35 ± 10.78 , mean \pm SD), who were admitted to psychiatric wards of the University of Frankfurt from February, 1990, to June, 1993. Diagnosis of catatonic syndrome was made according to criteria of Lohr and Wiesniwski (1987; see Appendix 1) and Rosebush et al (1990; see Appendix 2). Relying on a cluster of symptoms, as recommended by Gelenberg (1977), these scales, unlike others (Abrams and Taylor 1977; Taylor 1990), use a rather strict definition of catatonia. All patients had to be diagnosed as catatonic according to both criteria by two independent psychiatrists (GN, JW). Fourteen patients were classified as having excited catatonia and 23 patients with retarded catatonia.

Comorbid diagnosis was made according to DSM III/R

(APA 1987) by an independent psychiatrist using a structured clinical interview at discharge. All patients were classified as catatonic according to criteria of Lohr and Rosebush on the day of admission, whereas diagnosis according to DSM III/R was made at discharge. The patient sample consisted of the following DSM III/R diagnoses:

- Catatonic schizophrenia (295.2): 6
- Paranoid schizophrenia (295.3): 1
- Residual schizophrenia (295.6): 11
- Schizoaffective disorder (295.7): 4
- Major depression (296.2): 4
- Bipolar mania (296.4): 5
- Brief reactive psychosis (298.8): 2
- Dysthymia (300.4): 1

Moreover we had three catatonic patients with an associated organic disease: one with hypoxic brain disease and two with an encephalopathy due to acquired immunodeficiency syndrome (AIDS). According to the criteria of Lohr and Rosebush, these three patients were classified as catatonic.

According to their diagnosis, all patients were grouped into categories of affective ($n = 13$)/nonaffective ($n = 24$), schizophrenic ($n = 22$)/nonschizophrenic ($n = 15$), and residual schizophrenic ($n = 11$)/nonresidual schizophrenic, and nonschizophrenic ($n = 26$). Patients with Parkinson's disease and other movement disorders were excluded.

From 37 catatonic patients, 21 were neuroleptically untreated (at least 6 months off neuroleptics prior to admission): 18 had never received any neuroleptics and three patients were treated with haloperidol (2–18 mg) for an average duration of 2.1 ± 1.2 years. Sixteen patients had received neuroleptics: haloperidol (dose range 2–20 mg; average duration 3.2 ± 1.1 years) either on the day of admission (eight patients) or in the 6 months before admission (eight patients; average washout period: 1.8 ± 0.9 months). In addition, three of these patients received antidepressants (doxepin; dose range 50–200 mg, average duration 3.0 ± 1.5 months) and 2 patients were treated with lithium (dose range 200–600 mg, average duration 2.1 ± 1.2 years) in the 6 months prior to admission. Hence on the day of admission as well as in the 6 months before admission 21 catatonic patients were entirely unmedicated.

Seventeen healthy subjects (eight women, nine men, age: 32.0 ± 4.5 , means \pm SD) served as control group and were matched to catatonic patients with regard to age and sex.

On the day of admission our sample of 37 catatonic patients showed severe general psychopathology, measured by Global Assessment Scale (GAS: 10.3 ± 4.9 ; Endicott et al 1976) and Brief Psychiatric Rating Scale (BPRS: 60.2 ± 15.2 ; Overall and Gorham 1962).

Blood was obtained from antecubital vein between 8:00 and 8:30 AM, before initial medication, in catatonics as well as in controls. Blood samples were drawn in heparinized tubes, plasma was prepared by means of a refrigerated centrifuge, and stored at -60°C until determination of HVA and 3-hydroxy-4-methoxyphenylglycol (MHPG). By these means we tried to account for methodologic problems such as influencing variables on measurement of plasma HVA as well as the problem of peripheral or central origin of plasma HVA.

With regard to influencing variables, we tried to account for factors (Davidson et al 1987; Sack et al 1988; Amin et al 1992) such as circadian rhythm (collection of blood samples at 8:20–8:30 AM in all patients, if possible, and controls), food (12 hour overnight fast), activity (rest in bed the night before), and renal function (no patients or controls with abnormal renal function were included; Potter et al 1989). Due to later admission times it was not possible to collect blood samples at 8:20–8:30 AM in some patients ($n = 4$). We were not able to account for seasonal variations (Amin et al 1992) because our patients were admitted throughout the year.

With regard to central or peripheral origin of plasma HVA, we measured plasma MHPG as an index of peripheral noradrenergic activity (Degrell et al 1990; Amin et al 1992).

Biochemical Determinations

Plasma HVA concentrations were determined using high-pressure liquid chromatography (HPLC) methods as described by Seiler and Hiemke (1993) and MHPG in accordance with a method described by Sarre et al (1992). Inter- and intraassay coefficients of variation of both procedures were lower than 5%.

Statistical Analysis

All results were expressed as mean and standard deviation. Deviations were calculated by use of the Kolmogoroff-Smirnov goodness of fit test. Statistical significance was computed with the *t* test for random samples. All computations were executed with the Statistical Package for the Social Sciences-X statistics software.

Results

All results for each patient can be seen in Table 1; in Table 2 all plasma HVA and MHPG values are calculated for the different groups and subgroups.

The group of unmedicated catatonic patients ($n = 21$; 132.8 ± 105.9 pmol/mL) as well as the combined group of unmedicated and medicated catatonics ($n = 37$; 118.6 ± 80.9 pmol/mL) showed significantly increased concentrations of plasma HVA (see Table 2) compared to controls (80.1 ± 40.2 pmol/mL, $p < 0.0416$, *t* test for independent groups, two-tailed). Medicated catatonic patients ($n = 16$; 104.5 ± 56.0 pmol/mL) did not differ significantly from controls. The mean plasma HVA levels in plasma from unmedicated catatonic patients were higher than in the group of medicated patients (see Table 2), although this level did not reach statistical significance. Otherwise there were no significant differences between patients receiving different treatments.

Table 2 shows the plasma HVA levels of the different subgroups of catatonic patients: nonschizophrenic/schizophrenic, nonaffective/affective, and nonresidual schizophrenic and nonschizophrenia/residual schizophrenic subgroups. No significant differences between these subgroups were computed. Moreover, no significant differences between patients with excited and retarded catatonia could be found.

With respect to plasma MHPG, there were no significant differences among all catatonic patients (16.4 ± 10.7 pmol/mL), unmedicated catatonic patients (18.5 ± 12.3 pmol/mL), medicated catatonic patients (13.7 ± 7.8 pmol/mL), and controls (17.5 ± 7.2 pmol/mL) as well as among the above-mentioned subgroups of catatonic patients (see Table 2). Significant positive correlations were calculated between plasma HVA and MHPG in the groups of all catatonic patients ($p = 0.0007$) as well as in the group of control subjects ($p = 0.0021$; see Table 2).

No significant Pearson product moment correlations could be obtained between plasma HVA and MHPG on the one hand and scores of GAS, BPRS, and age and gender on the other hand.

Discussion

We found significantly higher plasma HVA levels in all catatonic patients as well as in untreated catatonics compared to healthy controls (see Table 2). Investigations of plasma HVA in catatonia have not been reported yet. Our results of elevated plasma HVA in catatonia confirms findings by Gjessing. Patients with periodic catatonia showed increased urinary HVA and dopamine levels during catatonic phases whereas in noncatatonic intervals HVA and dopamine levels were within the range of healthy controls (Gjessing 1974).

Investigation of plasma HVA levels in schizophrenia showed controversial results (Pickar et al 1984; Garcia et al 1989). Compared to healthy controls, some investigators found higher plasma HVA in patients with paranoid

Table 1. Plasma HVA, Demographic, and Psychopathological Variables in 37 Catatonic Patients

Patient	Age	Gender	DSM III/R Diagnosis	Catatonia Score	GAS	BPRS	Plasma HVA (pmol/mL)	Medication before admission
1	42	F	Organic	5E	8	65	47.7	None
2	23	F	295.6	6R	12	58	69.5	Neuroleptics
3	26	F	295.7	7E	5	57	214.3	None
4	44	M	295.2	11R	9	60	58.1	None
5	27	F	295.2	4E	10	73	65.7	None
6	24	F	296.4	8R	10	56	68.7	None
7	20	M	295.6	5E	8	68	200.4	None
8	55	F	295.2	7E	15	40	516.8	None
9	45	F	Organic	6R	8	50	75.0	None
10	41	M	295.6	5R	25	71	31.9	Neuroleptics
11	35	M	295.6	4R	5	42	73.2	Neuroleptics
12	23	F	296.4	8E	8	36	85.6	None
13	27	M	295.6	9E	8	32	516.8	None
14	29	M	296.2	12R	3	72	92.1	None
15	29	F	295.3	10E	8	48	43.0	Neuroleptics
16	28	F	295.2	8E	10	40	74.9	Neuroleptics
17	24	M	Organic	11R	8	28	129.4	None
18	44	M	295.7	9R	13	53	122.4	Neuroleptics + antidepressant
19	21	F	296.2	6R	10	72	134.6	None
20	29	M	295.7	4E	4	61	189.1	Neurolept + antidep. + lithium
21	29	F	295.2	7R	18	65	49.1	None
22	42	M	296.4	9E	5	91	65.0	Neuroleptics
23	27	F	296.4	10R	20	55	150.1	Neuroleptics
24	44	M	295.6	5R	5	64	69.5	Neuroleptics
25	18	M	298.8	4E	24	67	49.1	None
26	19	F	295.6	6R	1	70	76.8	Neuroleptics
27	32	F	295.2	7R	10	46	80.9	None
28	22	F	300.4	5E	12	37	84.6	None
29	28	F	295.6	12R	12	35	97.7	Neuroleptics
30	45	M	296.4	10R	10	67	252.7	Neuroleptics
31	26	F	298.8	11R	16	66	193.5	None
32	28	F	296.2	9R	8	71	92.2	None
33	28	M	295.6	10E	10	73	110.8	None
34	52	F	295.6	6R	10	69	96.2	Neuroleptics
35	33	M	295.6	9R	10	78	119.9	Neuroleptics
36	34	M	295.7	4R	8	83	82.4	Neurolept. + antidep. + lithium
37	31	F	296.2	8R	10	60	133.9	None

F, female; M, male; E, excited; R, retarded; DSM III/R, *Diagnostic and Statistical Manual*, 3rd ed. rev.; BPRS, Brief Psychiatric Rating Scale; GAS, Global Assessment Scale; HVA, homovanillic acid.

schizophrenia (Davis et al 1985; Davidson et al 1991) and lower plasma HVA levels in patients with residual schizophrenia (Karoum et al 1987; Davidson and Davis 1988). Other investigators found no significant differences in plasma HVA among paranoid schizophrenics, residual schizophrenics, and healthy controls (Pickar et al 1984; Chang et al 1990; Baker et al 1991). Hence it remains unclear whether plasma HVA differentiates schizophrenic patients from healthy controls (Amin et al 1992).

Due to these controversial results it is generally agreed in the literature that the baseline values of plasma HVA

may not account for the differences between paranoid and residual schizophrenia. Instead, changes in plasma HVA induced by neuroleptic treatment and withdrawal may be able to differentiate between paranoid and residual schizophrenia (Glazer et al 1989). Neuroleptic treatment induces a significant decline in plasma HVA in patients with paranoid schizophrenia, accompanied by a good therapeutic response, whereas neuroleptics do not influence plasma HVA in patients with residual schizophrenia and a poor therapeutic response (Kirch et al 1988; Chang et al 1990; Baker et al 1991; Davidson et al 1991).

Table 2. Plasma HVA and MHPG in Catatonia

Group	n	Plasma HVA (pmol/mL; mean \pm SD)	Plasma MHPG (pmol/mL; mean \pm SD)	Correlation (<i>p</i>)
Catatonia unmedicated	21	132.8 \pm 105.9	18.5 \pm 12.3	0.0640
Catatonia medicated	16	104.5 \pm 56.0	13.7 \pm 7.8	0.0053
Catatonia total	37	118.6 \pm 80.9	16.4 \pm 10.7	0.0007
Catatonia nonaffective	24	125.9 \pm 105.1	16.2 \pm 12.5	0.0015
Catatonia affective	13	179.4 \pm 139.7	16.5 \pm 6.9	0.0025
Catatonia nonschizophrenic	15	154.6 \pm 199.7	16.1 \pm 5.9	0.0059
Catatonia schizophrenic	22	130.6 \pm 115.3	16.3 \pm 13.5	0.0021
Catatonia nonresidual schizophrenic + nonschizophrenic	26	138.5 \pm 163.7	15.8 \pm 9.1	0.0058
Catatonia residual schizophrenic	11	152.9 \pm 141.3	17.1 \pm 14.0	0.0368
Controls	17	80.1 \pm 40.2	17.5 \pm 7.2	0.0021

HVA, homovanillic acid; MHPG, 3-hydroxy-4-methoxyphenylglycol; SD, standard deviation.

Our results showed no significant differences between medicated and unmedicated catatonic patients. There is, however, a tendency toward a decrease in plasma HVA in medicated catatonic patients. Whereas unmedicated catatonics differed significantly from controls there was no such significant difference between medicated catatonics and controls. Thus, like other investigators of schizophrenia (Pickar et al 1986; Davila et al 1988; Bowers et al 1989; Davidson et al 1991; Davis et al 1991), we found lower plasma HVA in neuroleptically treated patients than in neuroleptically untreated patients.

With regard to plasma HVA, we were neither able to differentiate the various diagnostic subgroups (schizophrenia/nonschizophrenia, affective/nonaffective, residual/nonresidual schizophrenia, and nonschizophrenia) nor to differentiate between excited and retarded catatonia. Hence our results might present the first evidence that catatonia meets the definition of a "syndrome," not only on phenomenological (Gelenberg 1976; Editorial 1986) but also on biochemical grounds. A syndrome is defined as a "group of symptoms and signs of disordered function, related to one another by means of some anatomic, physiologic, or biochemical peculiarity. It embodies a hypothesis concerning the deranged function. . . ." (Braunwald et al 1987).

Considering the methodological shortcomings, such as sample size, overrepresentation of schizophrenia, no control of influencing variables in some patients ($n = 4$), and the large standard deviations in our plasma HVA results, such a conclusion has to be regarded very cautiously and preliminary. Hence further investigations of plasma HVA and the dopaminergic system in patients with catatonic syndrome and different comorbid diagnosis are necessary.

As have other investigators of schizophrenia (Bjerkénstad et al 1985; Gattaz et al 1985; Chang et al 1990; Pickar et al 1990) we found significant correlations between plasma HVA and plasma MHPG in all groups. Moreover plasma MHPG, as an index of peripheral

noradrenergic activity, did not differ significantly between catatonic patients and healthy controls, whereas plasma HVA differed significantly. Hence it appears unlikely that a significant proportion of plasma HVA is derived from plasma MHPG (Amin et al 1992).

Conclusion

With regard to dopamine, catatonia seems to be paradoxical: On the one hand it results in symptoms (akinesia) as in Parkinson's disease and neuroleptic malignant syndrome (NMS), in which nigrostriatal dopamine levels seem to be decreased (Nisijima and Ishiguro 1990; Tohgi et al 1990). On the other hand, catatonia becomes often associated with schizophrenia, in which alterations in mesolimbic and mesocortical dopaminergic pathways are assumed (Davis et al 1991). Considering the three different dopaminergic systems (nigrostriatal, mesolimbic, mesocortical), co-occurrence, as postulated for schizophrenia by some authors (Davis et al 1991), of in- and decreased function in different dopaminergic pathways may be possible.

In the case of catatonic syndrome we suggest increased mesolimbic dopaminergic function, which, secondarily, may downregulate nigrostriatal dopamine as the regulatory part of the "motor loop" (cortico-striatal-pallidal-thalamic-cortical circuit; Alexander et al 1990) via n. accumbens and gl. pallidus internus (Northoff 1995). Such a model might explain our findings of increased plasma HVA, the often observed anxiety in catatonia (Rosebush and Mazurek 1992), akinetic motor symptoms as in Parkinson's disease, association with schizophrenia, and the therapeutic effectiveness of lorazepam (Rosebush et al 1990) (Salam and Kilizieh 1988; Rosebush et al 1990; Menza 1991): Lorazepam may interfere with the limbic system so that anxiety is relieved. Thereby it may modulate the "motor-loop" via n. accumbens such that motor

symptoms in catatonia become resolved (Frichhione 1985; Rosebush and Mazurek 1992; Northoff 1995).

An alternative model would assume an increased nigrostriatal dopaminergic function within the "motor loop." Animals, given the dopamine agonist amphetamine in increasing doses, showed first hyperkinesias and, later, with higher doses, hypokinesia, and, finally, complete akinesia (Lyon and Robbins 1975). Such a model would explain the co-occurrence of hyper- and hypokinesias in catatonia, but it remains questionable whether such an animal model can be transferred to catatonia in humans.

Appendix 1: Catatonic Criteria by Rosebush (1990)

Definition of Catatonic Signs Defined by Kahlbaum

Catatonic Sign	Definition
Immobility	Paucity or absence of spontaneous movements
Staring	Decreased frequency of blinking
Mutism	Inaudible whisper or absence of spontaneous speech
Rigidity	Increased muscle tone during passive movement of limbs
Withdrawal/refusal to eat	Turning away from examiner, no eye contact, refusal to take food or drink when offered
Posturing	Voluntary assumption and maintenance of an inappropriate or bizarre posture
Grimacing	Unusual or exaggerated spontaneous facial expression; Kahlbaum also referred to these as "spout spasms," "convulsive-type spasms," and "tics"
Negativism	Active resistance to instruction (e.g., patient asked to close or open eyes or mouth does the opposite)
Waxy flexibility (catalepsy)	The maintenance of a limb in any position in which it is placed by the examiner
Echolalia/echopraxia	The repetition or mimicking of the examiner's actions or words
Stereotypy	Aimless repetitive movements, often bizarre in nature
Verbigeration	The continuous and directionless repetition of single words or phrases

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Appendix 2: Catatonic Criteria by Lohr and Wiesniski (1987)

Tentative Criteria for the Diagnosis of Catatonia

- At least one of the following should be present:
 - Catalepsy
 - Positivism (such as automatic obedience, Mitmachen, Mitgehen)
 - Negativism
- At least two of the following should also be present:
 - Stereotypies
 - Mannerisms or grimacing
 - Bizarreries
 - Posturing
 - Echo phenomena
 - Excessive muscular tension
 - Mutism
 - Staring
- For a diagnosis of retarded or withdrawn catatonia, hypokinesia should dominate the clinical picture.
- For a diagnosis of excited catatonia, impulsiveness, combativeness, denudativeness, or other signs of excessive activity should dominate the clinical picture.

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